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Antibiotic and Antibiotic-Containing Drugs; Reissuance of Regulations

Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER C—DRUGS

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By virtue of the authority vested in the Secretary of Health, Education, and Welfare by the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463; 21 U.S.C. 357) and delegated to the Commissioner of Food and Drugs by the Secretary (25 F.R. 8625), the regulations for antibiotic and antibiotic-containing drugs are revoked, and Parts 141a, 141b, 141c, 141d, 141e, 146, 146a, 146b, 146c, 146d, 146e, and 147 are reissued as set forth below. This document includes amendments published in the FEDERAL REGISTER up to and including December 17, 1962.

SUBCHAPTER C—DRUGS

PART 141a—PENICILLIN AND PENICILLIN-CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

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Sec.
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141a.95 Penicillin-streptomycin-erythromycin ointment; penicillin-dihydrostreptomycin-erythromycin ointment.
141a.96 Penicillin-streptomycin - neomycin-polymyxin ointment; penicillin-dihydrostreptomycin - neomycin-polymyxin ointment.
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141a.99 Benzathine penicillin V for aqueous injection veterinary.
141a.100 Phenethicillin potassium (potassium α-phenoxyethyl penicillin).
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141a.103 Methicillin sodium.
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AUTHORITY: §§ 141a.1 to 141a.107 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 141a.1 Sodium penicillin, calcium penicillin, potassium pencillin; potency.

(a) *Cylinders (cups).* Use stainless steel cylinders with an outside diameter of 8 mm. (±0.1 mm.), an inside diameter of 6 mm. (±0.1 mm.), and a length of 10 mm. (±0.1 mm.).

(b) *Culture media.* Use ingredients that conform to the standards prescribed by the U. S. P. or N. F.

(1) Make nutrient agar for the seed layer and for carrying the test organism as follows:

Peptone	6.0 gm.
Pancreatic digest of casein	4.0 gm.
Yeast extract	3.0 gm.
Beef extract	1.5 gm.
Glucose	1.0 gm.
Agar	15.0 gm.
Distilled water, q. s	1,000.0 ml.

pH 6.5 to 6.6 after sterilization.

(2) Make nutrient agar for the base layer as follows:

Peptone	6.0 gm.
Yeast extract	3.0 gm.
Beef extract	1.5 gm.
Agar	15.0 gm.
Distilled water, q. s	1,000.0 ml.

pH 6.5 to 6.6 after sterilization.

(3) Make nutrient broth, for preparing an inoculum of the test organism, as follows:

Peptone	5.0 gm.
Yeast extract	1.5 gm.
Beef extract	1.5 gm.
Sodium chloride	3.5 gm.
Glucose	1.0 gm.
Dipotassium phosphate	3.68 gm.
Potassium dihydrogen phosphate	1.32 gm.
Distilled water, q. s	1,000.0 ml.

pH 7.0 after sterilization.

In lieu of preparing the media from the individual ingredients specified in paragraph (b) (1), (2), and (3) of this section, they may be made from a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such media. Minor modification of the individual ingredients specified in paragraph (b) (1), (2), and (3) of this section are permissible if the resulting media possess growth-promoting properties at least equal to the media described.

(c) *Working standard.* Keep the working standard (obtained from the Food and Drug Administration) at room temperature in tightly stoppered vials, which in turn are kept in larger stoppered tubes containing a suitable desiccant. Weigh out carefully in an atmosphere of 50 percent relative humidity or less between 4 and 5 milligrams of the working standard and dilute with sterile 1 percent phosphate buffer (pH 6.0) to make a stock solution of any convenient concentration. Keep this solution under refrigeration and use for 2 days only. From this stock solution make appropriate working dilutions.

(d) *Preparation of sample.* Dissolve the sample to be tested in 1.0 percent phosphate buffer, pH 6.0, to make an appropriate stock solution.

(e) *Preparation of plates.* Add 21 ml. of agar to each Petri dish (20 x 100 millimeters). Distribute the agar evenly in the plates and allow it to harden. Use the plates the same day they are prepared. The test organism is *Staphylococcus aureus* (American Type Culture Collection 6538P). Maintain the test organism on agar slants and transfer to a fresh agar slant about once a week. Prepare an inoculum for the plates by transferring the culture from the agar slant into broth and incubate at 32° C.–35° C. From 16 to 24 hours thereafter add 2.0 milliliters of this broth culture to each 100 milliliters of agar which has been melted and cooled to 48° C. Mix the culture and agar thoroughly and add 4 milliliters to each of the plates containing the 21 milliliters of the uninoculated agar. Tilt the plates back and forth to spread the inoculated agar evenly over the surface. Porcelain covers glazed on the outside are used. Place four cylinders on the agar surface so that they are at approximately 90° intervals on a 2.8 cm. radius. In so placing the cylinders drop them from a height of ½ inch, using a mechanical guide or device. A suspension of the test organism may be used in place of the broth culture described above in preparing the inoculum for the seeding of plates. Prepare such suspension as follows: Wash the organisms from an agar slant which has been incubated for 24 hours at 32° C.–35° C. and stored for 24 hours at room temperature with 2.0 milliliters of sterile physiological saline onto a large agar surface such as that provided by a Roux bottle containing 300 milliliters of agar. Spread the suspension of organisms over the entire agar surface with the aid of sterile glass beads. Incubate 24 hours at 32° C.–35° C. and store for 24 hours at room temperature. Wash the resulting growth from the agar surface with about 50 milliliters of sterile physiological saline. Standardize this suspension by determining the dilution which will permit 20 percent light transmission through a filter at 6500 Angstrom units in a photoelectric colorimeter. (In the preparation of the suspensions of the test organism on agar slants and Roux bottles, the 24-hour storage periods at room temperature may be omitted if the suspensions will permit 20-percent light transmission through a filter at 6,500 angstrom units in a photoelectric colorimeter). Determine by appropriate tests the quantity of this resulting dilution to be added to each 100 milliliters of agar, which has been melted and cooled to 48° C., for the secondary layer that will give sharp, clear zones of inhibition. The suspension may be used for 1 week.

(f) *Assay.* Use four plates for each sample. Fill one cylinder on each plate with a 1.0 unit per milliliter dilution, and one with a 0.25 unit per milliliter dilution, of the working standard. Add the estimated dilutions of 1.0 unit per milliliter and 0.25 unit per milliliter of the sample under test to the remaining two cylinders on each plate. Carefully place the plates in racks and incubate 16 to 18 hours at 32° C.–35° C. After incubation measure the diameter of each circle of inhibition to the nearest 0.5 millimeter using a colony counter with a millimeter scale etched into the supporting glass over the light source. Other measuring devices of equal accuracy may be used.

(g) *Estimation of potency and error.* (1) Use the accompanying chart (Chart 1) and nomograph (Chart 2) for estimating the potency and its error. To use the chart for estimating potency two values, namely, V and W, are required. For each plate calculate two values

$$v=(u_L+u_H)-(s_L+s_H)$$

and

$$w=(u_H+s_H)-(u_L+s_L)$$

where s_H and s_L are the diameters of the zones of inhibition in millimeters of the 1.0 unit and 0.25 unit dilutions of the standard, respectively, and u_H and u_L refer similarly to the corresponding dilutions of the sample under test. The value V is the sum of the v values for all plates and W is the sum of the w values for all plates. To estimate the potency locate the point on the chart corresponding to the values of V and W, and the potency can be read from the radial lines on the chart.

(2) The error of the assay is estimated by using the nomograph which requires five values, namely, the potency, V, W, Rv, and Rw. Rv (the range of the v's) is the highest value of v minus the lowest value of v obtained from the individual plates. Similarly, Rw is the difference between the highest and lowest w values. After obtaining these five values, connect with a straightedge the points corresponding to v and w on the respective scales on the right side of the nomograph. Mark with a pin or sharp-pointed pencil the intersection of the straightedge and the diagonal line of the nomograph. Move the straightedge so that it connects the value of Rw on its scale and the diagonal line at the point of the pin. The value for Q is thus determined by the scale value where the straightedge crosses the line labeled "Q". T is obtained by adding the squares of Q and Rv. On the left side of the chart connect the values of T and W with the straightedge and read the value of the ratio (error of assay-potency) where the straightedge intersects the scale of values for the ratio. This value multiplied by the potency equals the percentage error of the assay. The error of the assay calculated here estimates only how closely one assayist can check himself on any given set of dilutions of unknown and standard. It does not include any errors of weighing or errors due to variations in materials or subdivisions of a lot of penicillin.

The chart for determining potency should not be used for determinations of potency lower than 50 percent or higher than 150 percent of the standard. If the potency lies outside these limits, the assay should be repeated using a higher or lower dilution. The radial lines on the chart beyond these limits permit a rough estimation of potency from as low as 5 percent to as high as 1,000 percent when low values of W are found. If the value of V or W falls outside the limits of the chart, divide both V and W by the same proper number to bring them into the range of the chart and read the potency from the radial lines as before. If 11.4 Rw is greater than W, the slope of the assay does not differ significantly from zero and the assay is invalid. (The figure 11.4 was obtained by use of Student's "t" test for determining the significance of a slope.)

In certain laboratories it has been noted that with the 4 to 1 ratio, involving concentrations of 0.25 unit for the low dose, the zone of inhibition given by this dose may either be too small for accurate reading or have edges which are poorly defined. In order to permit the use of a higher concentration of penicillin for the low dose the third of the attached charts (Chart 3) may be used in assays in which the ratio of doses is 2 to 1, i. e., the high dose (sH) is twice the low dose (sL). As in the preceding chart (Chart 1), if the potency lies outside the limits of 50 percent to 150 percent the assay should be repeated, using a lower or higher dilution. The potencies beyond these limits are to be used for rough estimation purposes only. These extensions can also be used for four (or more) plate assays if both V and W are divided by the same proper number to bring them into the range of the chart. The error of the assay using the ratio of doses 2 to 1 is estimated by using the nomograph (Chart 2) in the same manner as described for the 4 to 1 ratio of doses. However, the resultant error of the assay derived in this manner must be divided by 2 to give the correct error of the assay for the 2 to 1 ratio of doses.

(h) *Assay by alternative methods.* The potency of the sample may also be determined by the iodometric method as described in § 141a.5(d), or by the standard-curve technique, using a single dose of standard and unknown. In the case of the standard-curve technique, dilute the sample to be tested to 1.0 unit per milliliter (estimated) in 1 percent phosphate buffer, pH 6.0. Place six cylinders on the inoculated agar surface so that they are at approximatly 60° intervals on a 2.8-centimeter radius. Use three plates for each sample and fill three cylinders on each plate with the 1.0 unit per milliliter standard and three cylinders with the 1.0 unit per milliliter (estimated) sample, alternating standard and sample. Incubate the plates for 16 to 18 hours at 32° C.–35° C. and measure the diameter of each circle of inhibition. Average the zone reading of the standard, and average the zone readings of the sample on the plates used. If the sample gives a larger average zone size than the average of the standard, add the difference between them to the 1.0 unit per milliliter zone size of the standard curve. If the average sample zone size is smaller than the standard value, subtract the difference between them from the 1.0 unit per milliliter zone size of the standard curve. From the curve read the concentration corresponding to these corrected values of zone sizes. Prepare concentrations for the standard curve by diluting aliquots of the standard stock solution with 1 percent phosphate buffer, pH 6.0, to give final concentrations of 0.64, 0.80, 1.0, 1.25, and 1.56 units per milliliter. Use three plates for each concentration except the 1.0 unit per milliliter concentration. Thus there will be a total of 12 plates. The 1.0 unit concentration is the reference point and is included on each plate. On each of three plates fill three cylinders with the 1.0 unit per milliliter standard and the other three cylinders with the concentration of the standard under test. Thus there will be thirty-six 1.0 unit per milliliter determinations and nine determinations for each of the other concentrations on the curve. Incubate the plates for 16 to 18 hours at 32° C.–35° C. and measure the diameter of each circle of inhibition. Average the readings of 1.0 unit per milliliter concentration and the readings of the concentration tested on each set of three plates, and average also all 36 readings of the 1.0 unit per milliliter concentration. The average of the 36 readings of the 1.0 unit per milliliter concentration is the correction point for the curve. Correct the average value obtained for each concentration to the figure it would be if the 1.0 unit per milliliter reading for that set of three plates were the same as the correction point. Thus, if in correcting the 0.8 unit per milliliter concentration, the average of the 36 readings of the 1.0 unit per milliliter concentration is 18 millimeters and the average of the 1.0 unit per milliliter concentration on this set of three plates is 17.8 millimeters, the correction is +0.2 millimeter. If the average reading of the 0.8 unit per milliliter concentration of these same three plates is 17.0 millimeters, the corrected value is then 17.2 millimeters. Plot these corrected values including the average of the thirty-six 1.0 unit per milliliter concentrations on two-cycle semilog paper, using the concentrations in units per milliliter as the ordinate (logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Draw the standard curve through these points, either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e,}{5}$$

$$H=\frac{3e+2d+c-a,}{5}$$

where:

L = calculated zone diameter for the lowest concentration of the standard curve,

H = calculated zone diameter for the highest concentration of the standard curve,

c = average zone diameter of 36 readings of the 1.0 unit per milliliter standard,

a, b, d, e = corrected average values for the 0.64, 0.80, 1.25, and 1.56 units per milliliter standard solutions, respectively.

Plot the values obtained for L and H and connect with a straight line.

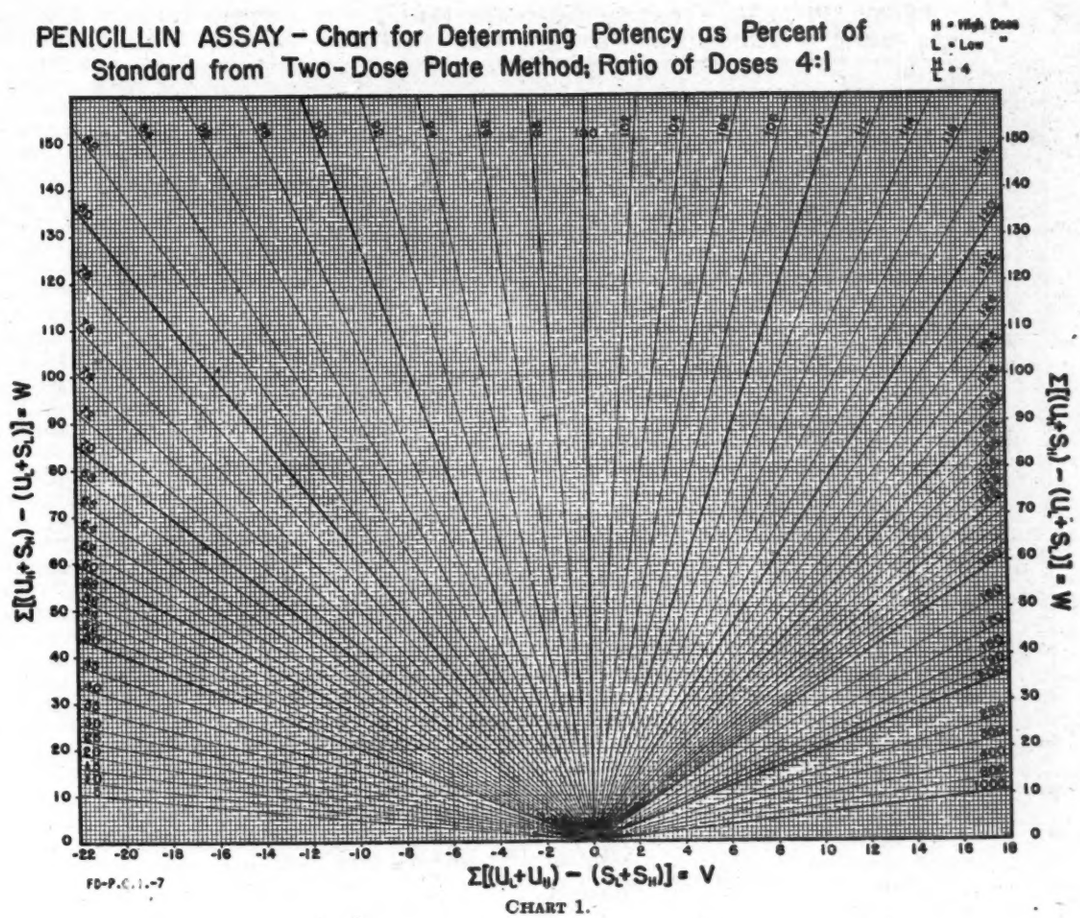
PENICILLIN ASSAY – Chart for Determining Potency as Percent of Standard from Two-Dose Plate Method; Ratio of Doses 4:1
H = High Dose
L = Low
H/L = 4
Σ[(UH+SH) – (UL+SL)] = W
Σ[(UL+UH) – (SL+SH)] = V
Σ[(UL+SH) – (UH+SL)] = W
FD-P.C.I.-7

CHART 1.

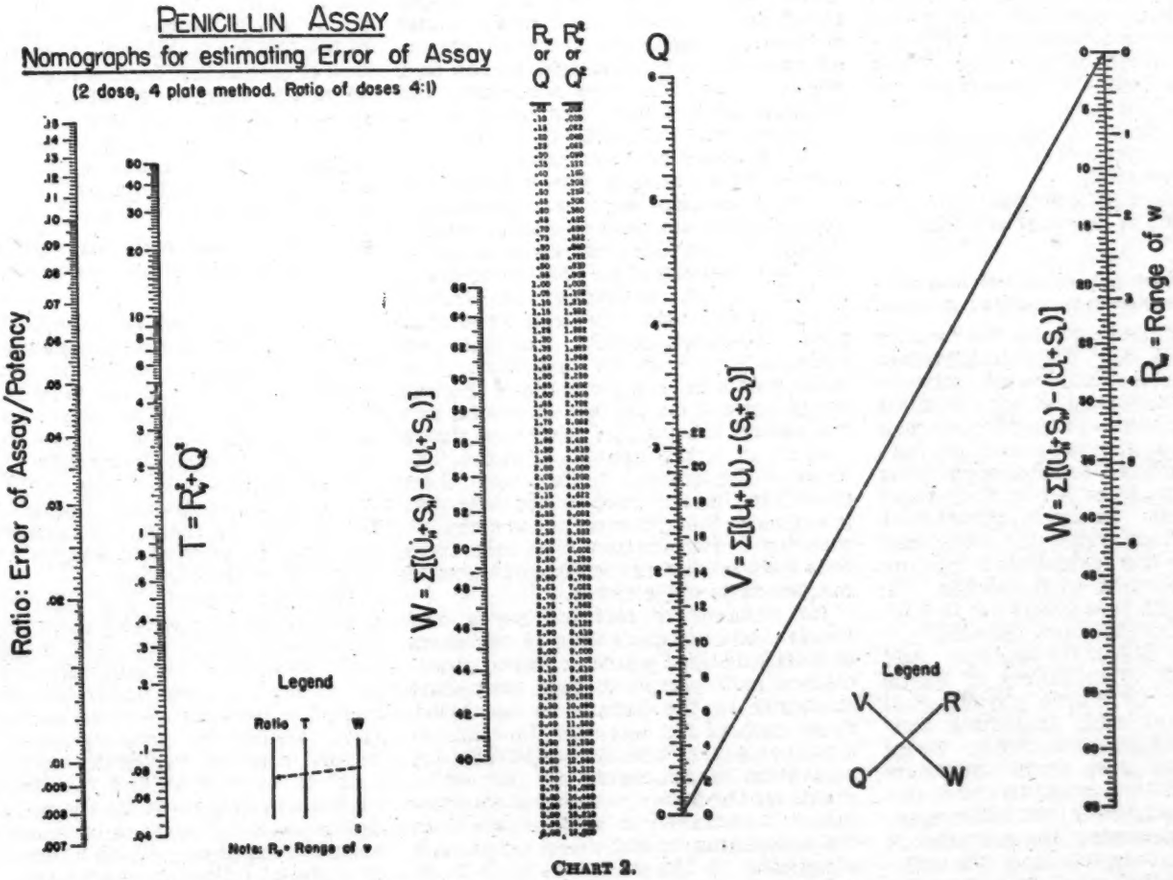

CHART 2.

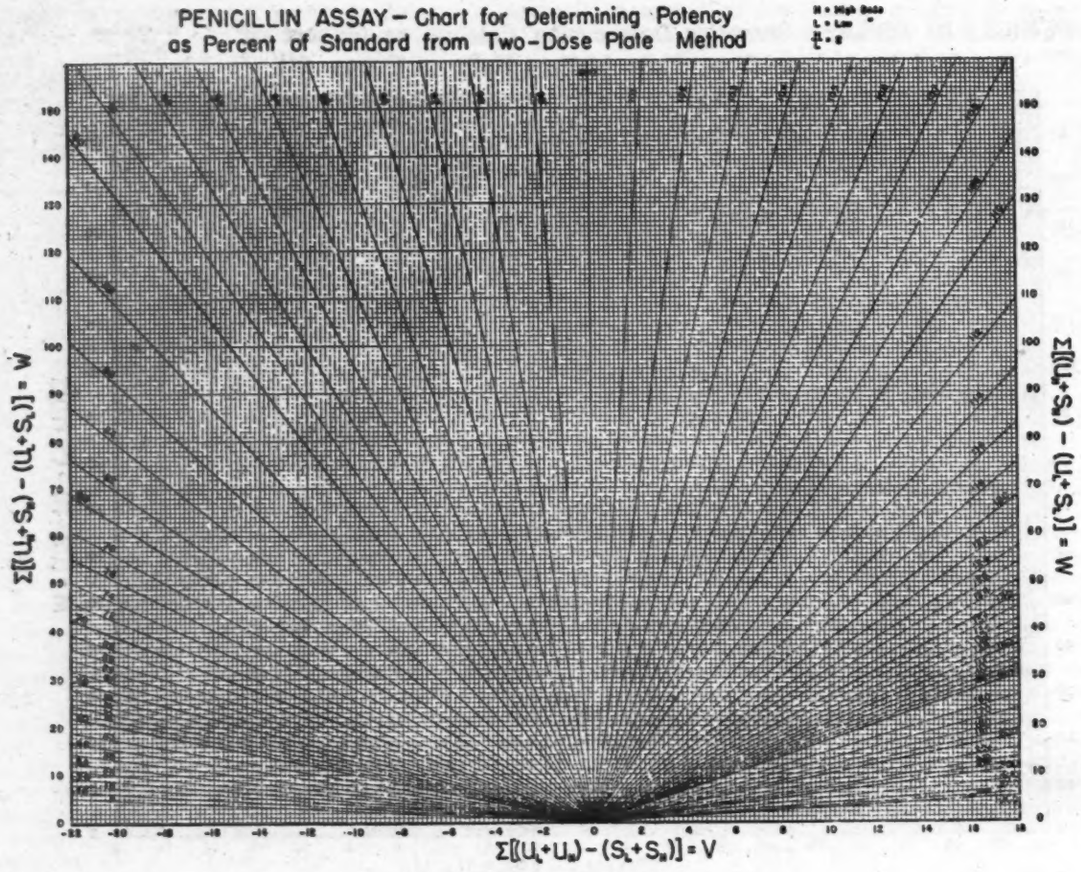
PENICILLIN ASSAY – Chart for Determining Potency as Percent of Standard from Two-Dose Plate Method
Σ[(U_H+S_H) – (U_L+S_L)] = W
Σ[(U_H+S_L) – (U_L+S_H)] = M
Σ[(U_L+U_H) – (S_L+S_H)] = V

CHART 3.

(i) *Potency.* The potency of sodium penicillin, calcium penicillin, and potassium penicillin is satisfactory when assayed by the methods described in this section if the immediate containers are represented to contain:

(1) 200,000 units or less and contain 85 percent or more of the number of units so represented;

(2) More than 200,000 units and contain 90 percent or more of the units so represented.

§ 141a.2 Sodium penicillin, calcium penicillin, potassium penicillin; sterility.

(a) *Culture medium.* In the test for bacteria, use U. S. P. fluid thioglycolate medium I or a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such medium and has growth-promoting, buffering, and oxygen-tension-controlling properties equal to or better than those of such medium. In the preparation of the medium from either the individual ingredients or any dehydrated mixture avoid contamination with calcium. In the test for molds and yeasts use U. S. P. Sabouraud Liquid Medium (Modified).

(b) *Conduct of test for bacteria.* Add not more than 10 milliliters of sterile distilled water, or sterile physiological salt solution, to each immediate container in the sample to be tested. From each of not less than seven immediate containers transfer aseptically the equivalent of approximately 300 milligrams, or the entire contents if the container is packaged to contain less than 300 milligrams, to individual tubes (38 x 200 millimeter size) each containing 75–100 milliliters of thioglycolate medium and sufficient penicillinase to completely inactivate the penicillin used in the test. (Prior to use, the tubes containing the medium with added penicillinase are incubated at 32° C.—35° C. for not less than 24 hours and examined for sterility.) After adding the penicillin to the tubes let them stand at room temperature for 2 hours, with frequent shaking. To one of such tubes add 1.0 milliliter of a 1:1,000 dilution of an 18–24 hour broth culture of M. pyogenes var. aureus (P. C. I.–209P and American Type Culture Collection 6538P). Incubate all tubes at 32° C.—35° C. for 5 days. The batch meets the requirements of the test for bacteria if on the first or second test the control tube and no other tube shows growth, or if the number of tubes (excluding the control tubes) that show growth in three or more consecutive tests is not more than 10 percent (to compensate for contamination that may have been induced during the test) of the total number of samples tested.

(c) *Conduct of test for molds and yeasts.* Add not more than 10 milliliters of sterile distilled water or sterile physiological salt solution to each immediate container in the sample to be tested. From each of not less than four immediate containers transfer aseptically the equivalent of approximately 300 milligrams, or the entire contents if the container is packaged to contain less than 300 milligrams, to individual tubes each containing 75–100 milliliters of U. S. P. Sabouraud Liquid Medium. Incubate all tubes at approximately 25° C. for 5 days. The batch meets the requirements of the test for molds and yeasts if on the first or second test no tube shows growth, or if the number of tubes that show growth in three or more consecutive tests is not more than 10 percent (to compensate for contamination that may have been induced during the test) of the total number of samples tested.

§ 141a.3 Sodium penicillin, calcium penicillin, potassium penicillin; pyrogens.

(a) *Temperature recording.* Use an accurate clinical thermometer or any other temperature-recording device of equal sensitivity that has been tested to determine the time necessary to reach the maximum reading. Insert the temperature-recording device into the rectum of the test animal to a depth of not less than 7.5 centimeters and allow sufficient time to reach a maximum temperature, as previously determined, before taking the reading.

(b) *Test animal.* Use healthy, mature rabbits, each weighing not less than 1500 grams and which have maintained their weight on an antibiotic-free diet for at least 1 week under the environmental conditions specified in this section. House the animals individually in an area of uniform temperature (±3° C. (±5° F.)) and free from disturbances likely to excite them. Do not use animals for pyrogen tests more frequently than once every 48 hours or prior to 2 weeks following their having been given a test sample that was adjudged

pyrogenic. One to 3 days before using an animal that has not been used for a test during the previous 2 weeks, condition it by conducting a sham test as directed under paragraph (c) of this section, omitting the injection.

(c) *Procedure.* Perform the test in an area where the animals are housed or under similar environmental conditions. On the day of the test, withhold all food from the animals being used until after completion of the test, except that access to water may be allowed, and determine the "control temperature" of each animal. In any one test use only those animals the control temperatures of which do not deviate by more than 1° C. from each other, and do not use any animal with a temperature exceeding 39.8° C. The control temperature recorded for each rabbit constitutes the temperature from which any subsequent rise following the injection of the material is calculated. Render the syringes, needles, and glassware free from pyrogens by heating at 250° C. for not less than 30 minutes or by any other suitable method. Warm the product to be tested to approximately 37° C. Dilute the sample with sterile, pyrogen-free distilled water to a concentration of 2,000 units per milliliter. Inject 1 milliliter per kilogram into an ear vein of each of three rabbits within 30 minutes subsequent to the control temperature reading. Record the temperature at 1, 2, and 3 hours subsequent to the injection. If no rabbit shows an individual rise in temperature of 0.6° C. or more above its respective control temperature, and if the sum of the three temperature rises does not exceed 1.4° C., the sample meets the requirements for the absence of pyrogens. If one or two rabbits show a temperature rise of 0.6° C. or more, or if the sum of the temperature rises exceeds 1.4° C., repeat the test, using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.6° C. or more, and if the sum of the eight temperature rises does not exceed 3.7° C., the sample meets the requirements for the absence of pyrogens.

§ 141a.4 Sodium penicillin, calcium penicillin, potassium penicillin; toxicity.

Inject intravenously each of five mice, within the weight range of 18 to 25 grams, with 0.5 milliliter of a solution of the sample prepared by diluting with sterile distilled water to approximately 4,000 units per milliliter. The injection should be made over a period of not more than 5 seconds. If no animal dies within 48 hours, the sample is nontoxic. If one or more animals die within 48 hours, repeat the test with five unused mice weighing 20 grams (±0.5 gram) each; if all animals survive the repeat test, the sample is nontoxic.

§ 141a.5 Sodium penicillin, calcium penicillin, potassium penicillin; moisture, pH, microscopical test for crystallinity.

(a) *Moisture.* In an atmosphere of about 10 percent relative humidity, transfer about 100 milligrams of the finely powdered sample to a tared weighing bottle or weighing tube equipped with a capillary-tube stopper, the capillary having an inside diameter of 0.20 millimeter–0.25 millimeter. Weigh the bottle or tube and place it in a vacuum oven without removing the stopper and dry at a temperature of 60° C. and a pressure of 5 millimeters of mercury or less for 3 hours. At the end of the drying period, fill the vacuum oven with air dried by passing it through a drying agent such as sulfuric acid or silica gel. Place weighing bottle or tube in a desiccator over a desiccating agent such as phosphorous pentoxide or silica gel, allow to cool to room temperature, and reweigh.

(b) *pH.* Dilute the sample to be tested with carbon-dioxide-free distilled water so that the resulting solution contains 30 milligrams per milliliter. Determine the pH of this solution at 25° C. using a pH meter equipped with a glass and a calomel electrode.

(c) *Microscopical test for crystallinity of sodium penicillin and potassium penicillin.* Mount in mineral oil and examine by means of a polarizing microscope. Crystalline penicillin shows resolvable particles which reveal the phenomena of birefringence (interference colors) and extinction positions on revolving the microscope stage. Crystalline penicillin also reveals diagnostic refractive indices when examined by the immersion method.

(d) *Heat stability*—(1) *Crystalline penicillin, crystalline penicillin G.* Store a weighed sample (approximately 30 milligrams) of crystalline penicillin in an unstoppered 50-milliliter Erlenmeyer flask for 4 days in an electric oven at 100° C.±1°. At the end of this period it does not show a loss of more than 10 percent of its original potency when determined as follows: Dilute a weighed sample (approximately 30 milligrams) with a 1-percent phosphate buffer at pH 6.0 to a concentration of approximately 1.2 milligrams per milliliter (2,000 units per milliliter). Add 2.0-milliliter aliquots to each of two 125-milliliter glass-stoppered Erlenmeyer or iodine flasks. To one add 2.0 milliliters of 1 *N* NaOH and allow to stand at room temperature for 15 minutes. At the end of this time add 2.0 milliliters of 1.2 *N* HCl and add 10 milliliters of 0.01 *N* I_2 (prepared from 0.1 *N* I_2 U. S. P.). (Equal volumes of 1 *N* NaOH and 1.2 *N* HCl when mixed give pH 1.0.) After 15 minutes, titrate the excess iodine, using 0.01 *N* $Na_2S_2O_3$. Toward the end of the titration add one drop of starch solution or about 5.0 milliliters of CCl_4. Continue the titration by the addition of 0.01 to 0.02-milliliter portions of 0.01 *N* $Na_2S_2O_3$, shaking vigorously after each addition. The end point is reached when the blue color of the starch-iodine complex is discharged or when the CCl_4 layer becomes colorless. To the second flask add 10 milliliters of 0.01 *N* I_2 and titrate immediately with 0.01 *N* $Na_2S_2O_3$ for the blank determination. Divide the difference in titers by a factor, F, which is the number of milliliters of 0.01 *N* I_2 absorbed by 1.0 milligram of sodium penicillin G working standard, to obtain the milligrams of penicillin sodium salt. Determine the factor F by actual standardization against the sodium penicillin G working standard, using the above method.

$$\text{Units of penicillin G per milligram} = \frac{\text{Difference in titers} \times \text{potency of FDA penicillin G working standard in units per milligram}}{\text{Sample weight (milligrams) in 2.0 milliliters} \times F}$$

$$\text{Percent loss of potency} = \frac{(\text{Original assay—assay after 4 days at 100° C.}) \times 100}{\text{Original assay}}$$

(2) *Crystalline penicillin O.* Proceed as directed in subparagraph (1) of this paragraph, except make the calculations as follows: Divide the difference in titers by a factor, *F*, which is the number of milliliters of 0.01 *N* I_2 absorbed by 1.0 milligram of the penicillin O working standard, to obtain the milligrams of potassium penicillin O. Determine the factor *F* by actual standardization against the penicillin O working standard.

$$\text{Units of penicillin O per milligram} = \frac{\text{Difference in titers} \times \text{potency of FDA penicillin O working standard in units per milligram}}{\text{Sample weight (milligrams) in 2 milliliters} \times F}$$

Penicillin O does not show a loss of more than 10 percent of its original potency.

(e) *Crystalline penicillin G*—(1) *Reagents.* The reagents described in subdivisions (i), (ii), and (iii) of this subparagraph are freshly prepared every three days and are of such quality that when used in this procedure with a known penicillin G not less than 97 percent of penicillin G is recovered.

(i) *Amyl acetate (iso-amyl acetate) solution.* Saturate the amyl acetate (boiling range 138.5°–141.5° C.) with the *N*-ethyl piperidine salt of penicillin G by adding 2 milligrams of the salt for each 1.0 milliliter of the solvent. Cool this solution to 0°–8° C. and filter it through a sintered-glass filter immediately before use.

(ii) *Acetone solution.* Saturate reagent grade acetone with the *N*-ethyl piperidine salt of penicillin G using 3 mg. of salt for each 1 milliliter of acetone. Cool this solution to 0°–8° C. and filter it through a sintered-glass filter immediately before use.

(iii) *N-ethyl piperidine solution.* *N*-ethyl piperidine (boiling range 129.5°–131.0° C.) should be stored in brown bottles in a refrigerator. Dilute 1.0 milliliter of this reagent with 4.0 milliliters of amyl acetate. Saturate this solution with the *N*-ethyl piperidine salt of penicillin G, using about 3 milligrams of the salt for each 1.0 milliliter of solution. Cool this solution to 0°–8° C. and filter it through a sintered-glass filter immediately before use.

(iv) *Phosphoric acid solution.* Prepare by dissolving 1.0 milliliter of reagent grade phosphoric acid (85 percent) in 4.0 milliliters of water. Cool to 0° to 8° C. and shake before using.

(v) *Silica gel.* Use dry silica gel (mesh size 6–16, Tyler standard). Place about 0.5 gram of the silica gel in a micro filter funnel (approximately 10-millimeter diameter) having a fritted-glass disc of medium porosity.

(2) *Procedure.* Accurately weigh from 60 to 70 milligrams of the sample to be tested in a glass test tube or glass vial of approximately 10 milliliters capacity. Add 2.0 milliliters of water to dissolve the penicillin and cool the solution to 0° to 5° C. Add 2 milliliters of the amyl acetate solution and 0.5 milliliter of the phosphoric acid solution, stopper and shake vigorously for approximately 15 seconds. Centrifuge to obtain a clear separation of the two layers (approximately 20 seconds). After centrifuging, remove as much of the amyl acetate layer as possible (usually about 1.7 milliliters–1.8 milliliters) with a 2-milliliter hypodermic syringe equipped with a suitable needle, and add it to the filter funnel containing the silica gel. Allow the amyl acetate to remain in contact with the silica gel for exactly 20 seconds, then apply suction and collect the filtrate in a small test tube placed in a suction flask surrounded by cracked ice. Pipette a 1.0-milliliter aliquot of the amyl acetate filtrate into a tared flat bottom glass tube (approximately 15 x 50 millimeters) containing 1.0 milliliter of the acetone solution and 0.5 milliliter of the *N*-ethyl piperidine solution. The time elapsing between acidification and the addition of the filtrate to the above reagents should not be more than 3 minutes. Place the glass tube containing this mixture in a large weighing bottle, stopper the bottle and allow to stand for not less than 2 hours in a refrigerator at 0° to 8° C. Remove the liquid from the precipitate by means of a tared micro filter stick and wash with a total of 1 milliliter of the acetone solution adding the latter by means of a hypodermic syringe equipped with a fine needle. Place the filter stick inside the glass tube, dry under vacuum at room temperature for not less than 1 hour, and weigh. (Save all *N*-ethyl piperidine penicillin G residues for saturating reagents.)

$$\text{Percent of sodium penicillin G} = \frac{\text{mg. } N\text{-ethyl piperidine penicillin precipitate} \times 159.3}{\text{Weight of sample mg.}}$$

$$\text{Percent of potassium penicillin G} = \frac{\text{mg. } N\text{-ethyl piperidine penicillin precipitate} \times 166.5}{\text{Weight of sample mg.}}$$

(f) *Penicillin K content.* Determine the content of penicillin K by the following method: Dilute a weighed sample or the contents of a vial with 0.3 *M* phosphate (Na_2HPO_4 and KH_2PO_4) buffer pH 6.0 to give a solution containing approximately 1,000 units/ml. In the case of calcium penicillin where a precipitate of calcium phosphate occurs, remove the precipitate by filtration and use the clear filtrate. Place a 15.0-milliliter aliquot of this solution in a 125-milliliter separatory funnel, add 30.0 milliliters of chloroform U. S. P. and shake for 1 minute. (Carry out all operations at room temperature.) Allow the mixture to stand with occasional swirling to settle the droplets of chloroform until the top layer is clear (usually about 10 minutes). Draw off all but about 2 milliliters of the lower chloroform layer through a small pledget of cotton into a glass-stoppered flask. Take a 4.0-milliliter aliquot of the original solution, a 4.0-milliliter aliquot of the buffer solution remaining in the separatory funnel and a 10.0-milliliter aliquot of the chloroform solution and determine the mg./ml. of penicillin in each by the iodometric assay procedure described in paragraph (d) of this section using 4.0 milliliters of the 1 *N* NaOH and 4.0 milliliters of the 1.2 *N* HCl for each of the above aliquots. Make blank determinations on the same size aliquots. Calculate the percent penicillin in the buffer layer and in the chloroform layer as compared to the original solution. The sum of these percentages should be 100%±2%. The percent penicillin K=(96.92+% in chloroform−% in buffer)×1.67. (The factors in the above formula are based on distribution coefficients of penicillin K and G between chloroform and aqueous phosphate buffer at pH 6.0.)

(g) *Penicillin G content of crystalline penicillin O.* Accurately weigh approximately 300 milligrams of the sample to be tested in a 250-milliliter Erlenmeyer flask, dissolve in 1.0 milliliter of 2.5 percent KOH solution, add with swirling 50.0 milliliters of 4.5 percent $KMnO_4$ solution and heat on the steam bath for 2 hours, covering the flask with a watch glass. Cool to room temperature and add 25.0 milliliters of 10 percent oxalic acid solution. When the reaction has ceased, add 15.0 milliliters of 18 *N* H_2SO_4 stepwise with agitation and cooling. Add 30.0 grams of NaCl and agitate until a clear, colorless solution is obtained. Transfer to a separatory funnel and extract with three portions of chloroform, 30 milliliters, 20 milliliters, and 10 milliliters in that order. Filter the extracts through a pledget of cotton previously moistened with chloroform and collect in a second separatory funnel. Add 50.0 milliliters of 0.1 *N* NH_4OH to the combined extracts, shake 5 minutes and allow the phases to separate for 10 minutes. Discard all but a few milliliters of the chloroform layer. Draw off the last few milliliters of chloroform and about 15.0 milliliters of the NH_4OH layer into a glass-stoppered test tube and centrifuge 2 minutes to obtain a clear aqueous layer. Prepare a blank by shaking 50.0 milliliters of 0.1 *N* NH_4OH with 60.0 milliliters of chloroform as described above. Determine the absorbance of the blank compared with 0.1 *N* NH_4OH at 220 mμ and 224mμ. Determine the absorbance of the sample at 220 mμ and 224 mμ compared with the blank. Calculate the quantity of benzoic acid in the solution from the equation:

$$x = \frac{R(A224) - (A220)}{RB - A}$$

where:

x = concentration of milligrams per milliliter of benzoic acid in sample.
A = absorbance per milligram of benzoic acid U.S.P. per milliliter of 0.1 *N* NH_4OH at 220 mμ.
B = absorbance per milligram of benzoic acid U.S.P. per milliliter of 0.1 *N* NH_4OH at 224 mμ.
$R = \frac{\text{absorbance of blank at 220 m}\mu}{\text{absorbance of blank at 224 m}\mu}$.
$A220$ = absorbance of sample at 220 mμ.
$A224$ = absorbance of sample at 224 mμ.

Calculate the quantity of penicillin G in the sample from the equation:

$$\frac{3.05 \times (50)(100)}{\text{Weight of sample in milligrams}} = \text{percent penicillin G.}$$

(h) *Penicillin O content.* (1) Accurately weigh approximately 100 milligrams of the sample in a 25-milliliter glass-stoppered test tube and add 5.0 milliliters of chloroform (previously washed with water) and 15 milliliters of distilled water. Place the tube in an ice bath for 5 minutes and then add 1.5 milliliters of 1 to 4 H_3PO_4. Shake the tube vigorously for 2 minutes, centrifuge for 1 minute to separate the layers, and withdraw the lower chloroform layer with the aid of a 10-milliliter hypodermic syringe equipped with a 3-inch needle. Superficially dry the chloroform by filtering through a pledget of cotton, using a U-shaped funnel to reduce evaporation during filtration. Collect the filtrate in a 5-milliliter glass-stoppered bottle and use within an hour. Place this chloroform solution in the absorption cell, which consists of two rock-salt plates with a 1.0-millimeter polyethylene spacer between them, clamped firmly in the cell holder. Adjust the amplification of a suitable infrared spectrometer to full-scale deflection for 1 μv., set the slit opening at 0.300 millimeter, and record the spectrum from 10.7 μ to 9.4 μ, taking a zero reading (shutter closed) at the beginning and at the end of the run. Calculate the baseline absorbance from the following equation:

$$A_b = \text{Log}_{10}\frac{I_b}{I_p}$$

where:

A_b = baseline absorbance.
I_b = distance from the zero line to the transmission peak at 10.3 μ.
I_p = distance from the zero line to the maximum absorption of the band at 10.1 μ.

The absorptivity, a, of the sample in the particular cell being used is calculated as follows:

$$a = \frac{A_b}{\text{Weight of sample}}.$$

Using an accurately weighed sample of about 100 milligrams of the potassium penicillin O working standard in the above procedure, determine its absorptivity in the same cell. Obtain the per-

cent penicillin O in the sample under test by the following calculation:

$$\frac{a\ (\text{sample})}{a\ (\text{standard})} \times 100 = \text{percent potassium penicillin O.}$$

$$\frac{a\ (\text{sample})}{a\ (\text{standard})} \times 95.6 = \text{percent sodium penicillin O.}$$

(2) If the sample is potassium penicillin O, the following method may be used: Grind the sample to a uniform powder, using a mortar and pestle. Weigh, by difference, 100 milligrams to 150 milligrams of liquid petrolatum into an agate mortar. Divide the actual weight of the liquid petrolatum by three, and add exactly this amount of the powdered penicillin O to the liquid petrolatum in the mortar. Mix with a small spatula and then mull thoroughly with the pestle until a uniform consistency is obtained. Use two circular rock-salt plates, each 2 inches in diameter, as the absorption cell. Place a small drop of the mull in the center of one of the rock-salt plates. Place a brass spacer, 0.0036-thick, on the plate. (This spacer is cut in the shape of a circular gasket with a 1-inch center hole and a slit to permit the escape of air when the two plates are pressed together.) Put on the top salt plate gently and slowly squeeze together to spread the mull uniformly. Clamp the two plates firmly together in a metal cell holder. (The cell holder consists of two metal plates, one containing a rectangular center slit ¼-inch wide x ⅝-inch long, the other with a center hole 1 inch in diameter. The two plates are clamped together by means of threaded studs and nuts.) Examine the assembled cell by holding it up to the light. It should appear smooth, free of any air bubbles, and not in contact with the spacer. Place the cell in a suitable infrared spectrophotometer. Adjust the amplification of the spectrometer to full-scale deflection for 1 μv., set the slit opening to about 0.300, and run the spectrum from 9.4 μ to 10.7 μ, using an automatic slit-control mechanism and taking a zero reading (shutter closed) at the beginning and at the end of the run. Draw a baseline between two points, one on each side of the analytical band (10.1 μ), and calculate the baseline absorbance, using the following equation:

$$A_b = \log_{10}\frac{I_b}{I_p}$$

where:

I_p = baseline absorbance.
A_b = distance from the zero line to the maximum absorption of the band.
I_b = distance from the zero line to the baseline, measured at the same wavelength as I_p.

Using known mixtures of penicillin G working standard and penicillin O working standard, prepare a standard curve by plotting the baseline absorbance values obtained against the percent penicillin O. Obtain the percent penicillin O in the sample under test from this standard curve.

§ 141a.6 Sodium penicillin, calcium penicillin, potassium penicillin; penicillin X.

Dissolve the contents of a 100,000 unit ampul in about 20 milliliters of ice cold distilled water. Transfer quantitatively to a 100-milliliter volumetric flask, rinsing the ampul with small portions of ice cold water and make to 100 milliliters. Pipette a 50.0-milliliter aliquot into a 125-milliliter separatory funnel, then add 50.0 milliliters of cold chloroform and shake the mixture. Add an amount of approximately 1 *N* H_2SO_4 to bring the pH of the aqueous layer to 2.0. (The amount of 1 *N* H_2SO_4 to be added is calculated by titrating a separate 5.0-milliliter aliquot of the 100-milliliter dilution to pH 2.0 using a suitable pH meter.) Shake the mixture vigorously for one minute. Allow the layers to separate and filter the chloroform through a small pledget of cotton, moistened with chloroform, into a second 125-milliliter separatory funnel. Shake the acid aqueous solution with a second 50.0 milliliters of cold chloroform and, when the layers have separated, withdraw the chloroform through the same filter into the second separatory funnel. Immediately neutralize the acid aqueous solution, containing the penicillin X, with 0.1 *N* NaOH to pH 6.5 to 7.0 using the pH meter and make to 100 milliliters with water. Make appropriate dilutions in 1 percent phosphate buffer at pH 6.0 and assay as directed in § 141a.1 (f) or (h). Shake the combined chloroform extracts, containing any penicillin G, etc., with small successive portions of cold $NaHCO_3$ solution (0.1 percent), until the combined $NaHCO_3$ extracts give a pH of 7.0, and make to 100 milliliters with water. Make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. Assay these last dilutions as directed in § 141a.1 (f) or (h). The potency of the penicillin X fraction plus potency of the penicillin G, etc., fraction should approximate that of the potency of the original solution. All of the above extractions should be carried out in a cold room.

§ 141a.7 Penicillin in oil and wax.

(a) *Potency.* Proceed as directed in § 141a.1 except paragraph (i) thereof and, in lieu of the directions in § 141a.1 (d) prepare sample as follows: Liquefy the sample by warming, thoroughly mix, and withdraw 1.0 milliliter using a sterile syringe equipped with an 18-gauge needle. Transfer to a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake the separatory funnel vigorously to bring about complete mixing of the material with the ether. Shake with a 25-milliliter portion of 1 percent phosphate buffer at pH 6.0. Remove the buffer layer and repeat the extraction with three 25-milliliter quantities of buffer. Combine the extracts and make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. The sample may also be prepared by transferring aseptically 1.0 milliliter of the penicillin in oil and wax to a blending jar containing 100 milliliters of 1 percent phosphate buffer at pH 6.0. Using a high-speed blender, blend this mixture for 1 minute and then make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. If the label represents the potency of the penicillin in oil and wax as 200,000 units per milliliter or less, it is satisfactory if it is 85 percent or more of the potency so represented; if represented as more than 200,000 units per milliliter, it is satisfactory if it is 90 percent or more of the potency so represented.

(b) *Sterility.* Transfer aseptically directly to the tubes of the medium the entire contents of single-dose containers or the equivalent of approximately 300 milligrams (activity) from each multiple dose container, and proceed as directed in § 141a.2.

(c) *Moisture*—(1) *Reagents*—(i) *Karl Fischer reagent.* Preserve the reagent in glass-stoppered bottles and use from an all glass automatic burette, protecting the solution from the moisture in the air.

(ii) *Water-methanol solution.* Use methanol containing approximately 1 mg. of water per milliliter. Store the solution in a glass bottle attached to an automatic burette and protect from moisture in the air at all times.

(2) *Standardization of Karl Fischer reagent.* Add a known volume of the Karl Fischer reagent to a suitable titrating vessel which has been previously dried at 105° C. and cooled in a desiccator. Introduce a mechanical stirrer and two platinum electrodes which are connected to a suitable electrometric apparatus for measurement of the endpoint. Start the stirrer and titrate with the water-methanol solution until the endpoint is reached. Calculate the milliliters of Karl Fischer reagent equivalent to each milliliter of water-methanol.

Add an accurately weighed quantity of water (approximately 50 milligrams) to a dry titrating vessel, add an excess of the Karl Fischer reagent and back titrate with the water-methanol solution as above. Calculate the milligrams of water equivalent to each milliliter of the Karl Fischer reagent. Standardize the Karl Fischer reagent in this manner daily.

$$e = \frac{w}{v_1 - v_2 f}$$

where

e = milligrams of water equivalent to 1 ml. Karl Fischer reagent.
w = weight of water in milligrams.
v_1 = volume of Karl Fischer reagent used.
v_2 = volume of methanol used.
f = volume ratio of Karl Fischer reagent to water-methanol solution.

(3) *Procedure.* Transfer 1.0 milliliter of the penicillin in oil and wax to a dry titrating vessel, add 10 milliliters of dry chloroform and an excess of the Karl Fischer reagent and back titrate with the water-methanol solution until the endpoint is reached. Transfer 10 milliliters of the dry chloroform used to a dry titrating vessel, add an excess of Karl Fischer reagent, and titrate with the water-methanol as above. Calculate the milliliters of Karl Fischer reagent equivalent to 10 milliliters of chloroform.

$$\text{Percent moisture} = \frac{(v_1 - v_2 f - b) \times e \times 100}{s \times 1000}$$

where

b = milliliters Karl Fischer reagent equivalent to 10 ml. of chloroform
s = volume of the sample in milliliters.

(d) *Measurement of penicillin particle size.* Vigorously shake the container to

obtain an even suspension of the penicillin particles and immediately withdraw therefrom approximately 0.5 milliliter of the drug into a clean, dry, tuberculin syringe using a dry 18-gauge needle. Discard approximately the first 5 drops of the mixture extruded from the needle and then extrude approximately 1 minim of the remaining mixture into a test tube containing 3 to 4 milliliters of light mineral oil. Thoroughly mix the contents of the tube and by means of a bacteriological loop (2 millimeters inside diameter, 22 gauge wire), immediately place one loopful of the suspension on each ruled chamber of a bright line hemocytometer. (It is not necessary to use a cover slip.) Confirm by means of the low power objective of the microscope the even distribution of particles over the ruled areas of both chambers and repeat with another loopful of the suspension if even dispersion is not obtained.

Use a magnification of 430 or 440 diameters and a calibrated ocular micrometer to measure the penicillin particles. For the purpose of measurement and calculation, the predominant type of crystals observed shall be considered to represent the type of crystals present and the thickness and density of all particles shall be considered constant. Center a large penicillin particle in the microscopic field; measure the particle and all other particles in the field and repeat this operation on other fields until at least 200 particles are measured. Particles of less than 5 microns in length are disregarded. The grouping of the particles by length, the midpoint, the ratio of the midpoints, and the square of the ratio of the midpoints for each group are tabulated below:

Group	Length in microns	Midpoint	Ratio of midpoints	(Ratio)²
1	5-14	9.5	1.00	1.00
2	15-29	22.0	2.31	5.34
3	30-49	39.5	4.16	17.31
4	50-69	59.5	6.26	39.19
5	70-99	84.5	8.89	79.03
6	100-149	124.5	13.10	171.61
7	150-199	174.5	18.36	337.09
8	200-249	224.5	23.63	558.38
9	250-300	275.0	28.95	838.10

Calculate the percent particles in each group from the total number measured. Determine the percent relative weight for each group as follows:

Plate type particles. Relative weight=(ratio)²×% of total particles in group.

$$\%\ \text{relative weight} = \frac{\text{relative weight} \times 100}{\text{total relative weight}}$$

Rod-shaped particles. In the case of rod-shaped particles measure the width as well as the length.

Relative weight=ratio × average width × % of total particles in group

$$\%\ \text{relative weight} = \frac{\text{relative weight} \times 100}{\text{total relative weight}}$$

When examined by the method described in this section not less than 50 percent of the total relative weight of the penicillin in the drug consists of penicillin having a particle size of not less than 50 microns in length.

§ 141a.8 Penicillin ointment.

(a) *Potency.* Proceed as directed in § 141a.1, except paragraph (i) of that section, and in lieu of the directions in § 141a.1(d), prepare the sample by one of the following techniques:

(1) *Extraction.* Place a representative portion of the sample (usually approximately 1 gram, accurately weighed) or the entire contents of a single-dose container in a separatory funnel containing 50 milliliters of peroxide-free ether. If the sample consists of substantially more than 1 gram, use 100 milliliters of peroxide-free ether. Shake the sample and ether until homogeneous. Add 25 milliliters of 1-percent phosphate buffer, pH 6.0, and shake. If the sample consists of substantially more than 1 gram, use 50 milliliters of buffer. Allow the layers to separate. Remove the buffer layer and repeat the extraction with new portions of buffer at least three times and any additional times necessary to ensure complete extraction of the antibiotic. Combine the extractives and make the proper estimated dilutions with buffer.

(2) *Blending.* Place an accurately weighed representative portion of the sample (usually approximately 1 gram), or the entire contents of a single-dose container, in a blending jar containing 1.0 milliliter of polysorbate 80 and sufficient 1-percent phosphate buffer, pH 6.0, to give a final volume of 200 milliliters. If the sample consists of substantially more than 1 gram, use sufficient buffer to give a final volume of 500 milliliters. Using a high-speed blender, blend the mixture for 2 minutes and then make the proper estimated dilutions with buffer. Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c), using a weighed sample of approximately 1 gram dissolved in 10 milliliters of a mixture of equal parts of dry chloroform and carbon tetrachloride, but in lieu of calculating the milliliters of Karl Fischer reagent equivalent to 10 milliliters of chloroform, determine the milliliters of reagent equivalent to 10 milliliters of the mixture of chloroform and carbon tetrachloride.

§ 141a.9 Penicillin tablets.

(a) *Potency*—(1) *Tablets that do not contain procaine penicillin G, benzathine penicillin G, penicillin V, or potassium penicillin V.* Proceed as directed in § 141a.1, except § 141a.1 (i), and in lieu of the directions in § 141a.1(d) prepare the sample by one of the following methods:

(i) *Grinding.* Grind a representative number of tablets (usually 5 to 12), using a mortar and pestle. Transfer all the powder or a weighed aliquot of the powder to an appropriate volumetric flask and make to mark by adding sufficient phosphate buffer, and shake thoroughly. Make the proper estimated dilutions in 1 percent phosphate buffer, pH 6.0.

(ii) *Blending.* Place a representative number of tablets (usually 5 to 12) in a blending jar and add thereto approximately 200 milliliters of a 500-milliliter quantity of 1 percent phosphate buffer, pH 6.0. After blending for 1 minute with a high-speed blender, add the remainder of the 500 milliliters of buffer. Blend again for 1 minute and make the proper estimated dilutions in 1 percent phosphate buffer, pH 6.0.

(iii) *Dissolving.* If the tablets dissolve readily, dissolve a representative number of tablets (usually 5 to 12) in 1 percent phosphate buffer, pH 6.0, and make the proper estimated dilutions in 1 percent phosphate buffer, pH 6.0.

(2) *Tablets that contain benzathine penicillin G.* Proceed as directed in § 141a.1, except § 141a.1(i), and in lieu of the direction in § 141a.1(d) prepare the sample as follows: Grind 6 tablets, using a mortar and pestle, and add sufficient formamide or dimethylformamide (previously adjusted, if necessary, to pH 6 to 7 with a few drops of concentrated H_2SO_4 per liter) to give a concentration of not more than 15,000 units per milliliter. Allow to stand for ½ hour, with frequent agitation, then make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. The sample may also be prepared by one of the following methods: Place 6 tablets in a blending jar containing 100 milliliters of a 500-milliliter quantity of redistilled methyl alcohol. After blending for 1 minute with a high-speed blender, add the remainder of the 500-milliliter quantity of redistilled methyl alcohol. Blend again and make the proper estimated dilutions, using 1.0 percent phosphate buffer, pH 6.0, or grind a representative number of tablets (usually 5 to 12), using a mortar and pestle. Add sufficient redistilled methyl alcohol to the powder, or a weighed aliquot of the powder, to give a concentration of 2,000 units to 5,000 units per milliliter. Allow to stand for ½ hour, with frequent agitation, then dilute with sufficient 1.0 percent phosphate buffer, pH 6.0, to give a stock solution of not less than 200 units per milliliter. Make the proper estimated dilutions, using 1.0 percent phosphate buffer, pH 6.0, to give a concentration of 1.0 unit per milliliter. If the iodometric assay method is used, proceed as directed in § 141a.84(a)(1).

(3) *Tablets that contain procaine penicillin G.* Proceed as directed in § 141a.1, except § 141a.1(i), and in lieu of the directions in § 141a.1(d), prepare the sample as follows: Grind a representative number of tablets (usually 5 to 12) using a mortar and pestle. To the powder, or a weighed aliquot of the powder, add sufficient redistilled methanol to give a concentration of 10,000 to 100,000 units per milliliter. Agitate thoroughly and dilute further with sufficient 1 percent phosphate buffer, pH 6.0, to give a concentration of 2,000 units per milliliter (estimated) if the iodometric assay method is used, or a concentration of 1.0 unit per milliliter (estimated) if the bioassay method is used.

(4) *Tablets that contain penicillin V.* Using the penicillin V working standard as the standard of comparison, proceed as directed in subparagraph (3) of this paragraph.

(5) *Tablets that contain potassium penicillin V.* Using the penicillin V working standard as the standard of comparison, proceed as directed in subparagraph (1) of this paragraph.

The average potency of penicillin tablets is satisfactory if they contain not less than 85 percent of the number of units per tablet that they are represented to contain.

(b) *Moisture.* Use 4 tablets and proceed as directed in § 141a.5(a), except that if they contain benzathine penicillin G or penicillin V proceed as directed in § 141a.26(e).

(c) *Disintegration time*—(1) *Uncoated tablets.* Proceed as directed in the U.S.P., using simulated gastric fluid test solution. The tablets are satisfactory if they disintegrate within 1 hour.

(2) *Plain coated tablets.* Proceed as directed in the U.S.P. If the tablets have not distintegrated after 30 minutes in the gastric fluid, use simulated intestinal fluid for an additional 30 minutes. The tablets are satisfactory if they disintegrate within 1 hour.

§ 141a.10 Potassium penicillin V (potassium penicillin V salt).

(a) *Potency.* Using the penicillin V working standard as the standard of comparison, proceed as directed in § 141a.1.

(b) *Toxicity.* Proceed as directed in § 141a.81 (b).

(c) *Moisture.* Proceed as directed in § 141a.5 (a) or § 141a.26 (e).

(d) *pH.* Proceed as directed in § 141a.5 (b), using an aqueous solution prepared by adding 30 milligrams per milliliter.

(e) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(f) *Penicillin V content.* Accurately weigh approximately 50 milligrams of the sample, dissolve in 0.1 *N* NaOH solution, and make to 100 milliliters with 0.1 *N* NaOH solution. Determine the absorbance of the sample at the absorption peak at 275 mμ using a suitable ultraviolet spectrophotometer and quartz cells. Set the instrument to 100-percent transmission with 0.1 *N* NaOH solution. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 240 mμ to 290 mμ. If a nonrecording instrument is used, determine the absorbance (of a solution containing 20 milligrams per 100 milliliters) at the 275 mμ absorption peak, using a slit width of 0.5 millimeter or less. (The exact position of the peak should be determined for the particular instrument used.)

$$\text{Percent potassium penicillin V} = \frac{\text{Absorbance at 276 m}\mu \times 100{,}000 \times 100}{\text{Milligrams of sample (in 100 milliliters)} \times a_{vs} \times 90.2}$$

where:

a_{vs} = absorptivity (1%, 1 cm.) of the penicillin V working standard similarly treated.

90.2 = percentage of penicillin V in pure potassium penicillin V.

§ 141a.11 Penicillin with aluminum hydroxide gel.

(a) *Sodium penicillin, calcium penicillin, potassium penicillin.* Proceed as directed in §§ 141a.1, 141a.2, 141a.4, and 141a.5 (a) and (b); if crystalline penicillin, § 141a.5 (c), (d) and (f); and if crystalline penicillin G, § 141a.5(e).

(b) *Aluminum hydroxide gel.* Thoroughly shake the aluminum hydroxide gel and transfer aseptically 1.0 and 0.1-milliliter portions in triplicate to sterile Petri dishes. Pour into each Petri dish 20 milliliters of nutrient agar, described in § 141a.1 (b) (1), which has been melted and cooled to 48° C. Thoroughly mix the aluminum hydroxide and melted agar. Allow the agar to solidify, invert the Petri dishes, and incubate for 48 hours at 32° C.–35° C. Count the number of colonies appearing on the plates and calculate therefrom the number of viable bacteria per milliliter of the aluminum hydroxide gel.

§ 141a.12 Penicillin troches.

(a) *Potency.* Proceed as directed in § 141a.1, except paragraph (i) thereof and, in lieu of the directions in § 141a.1 (d), prepare sample as follows:

(1) If the troche does not contain a masticatory substance, proceed as directed in § 141a.9 (a).

(2) If the troche contains paraffin as a masticatory substance, place five troches in a separatory funnel containing 75 ml. of *N*-hexane; shake until the troches are dissolved. Shake with a 25-milliliter portion of 1 percent phosphate buffer at pH 6.0. Remove the buffer layer and repeat the extraction with three 25-milliliter quantities of buffer. Combine the extracts and make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0.

(3) If the troche contains gum as a masticatory substance, cut each of five troches into fine pieces and place in a glass blending jar containing 100 milliliters of a 50 percent acetone-water solution. Using a high-speed blender, blend for 3 to 5 minutes. Add an additional 100 milliliters of a 50 percent acetone-water solution to the blender and blend for an additional 3 to 5 minutes, and then make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0.

The average potency of the troche is satisfactory if it contains not less than 85% of the number of units it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a), or if it contains a masticatory substance proceed as directed in § 141a.7 (c), using 1.0 to 2.0 grams dissolved in 10 milliliters of dry chloroform.

§ 141a.13 Penicillin dental cones.

(a) *Potency.* Proceed as directed in § 141a.1, except paragraph (i) thereof and, in lieu of the directions in § 141a.1 (d), prepare sample using 5 cones as directed in § 141a.9(a). The average potency of the cone is satisfactory if it contains not less than 85 percent of the number of units per cone it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.14 Penicillin with vasoconstrictor.

(a) *Penicillin used in the packaged combination*—(1) *Potency.* Unless it is penicillin tablets, proceed as directed in § 141a.1. If it is penicillin tablets, proceed as directed in § 141a.9(a).

(2) *Toxicity, moisture, pH, crystallinity, heat stability, penicillin G content.* Proceed as directed in §§ 141a.4 and 141a.5.

(b) *Dry mixture of penicillin with vasoconstrictor; potency, moisture.* Proceed as directed in §§ 141a.1 and 141a.5 (a).

§ 141a.15 Penicillin for surface application.

(a) *Potency.* Proceed as directed in § 141a.9(a) using the contents of 12 immediate containers.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.16 Tablets aluminum penicillin.

(a) *Potency.* Proceed as directed in § 141a.9 (a), using citrate buffer at pH 6.3 for making working dilutions of the working standards and for the sample under test in lieu of phosphate buffer. The citrate buffer is of the following composition:

	Grams
Citric acid	52.9
Sodium hydroxide (pellets)	26.25
Sodium citrate	988.0

Make up to 4000 ml. with distilled water.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

(c) *Disintegration time.* Proceed as directed in § 141a.9(c).

§ 141a.17 Penicillin sulfonamide powder.

(a) *Potency.* Proceed as directed in § 141a.9 (a), except prepare the samples as follows: Accurately weigh 0.5 gram from each of the immediate containers and dissolve in 100 milliliters of 1.0 percent phosphate buffer, pH 6.0. From this solution make the proper estimated dilutions in 1.0 percent phosphate buffer at pH 6.0.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

(c) *Sterility.* Transfer aseptically directly to the tubes of the medium approximately 0.5 gram from each container tested, and proceed as directed in § 141a.2.

§ 141a.18 Penicillin vaginal suppositories.

(a) *Potency.* Proceed as directed in § 141a.1 except paragraph (i) thereof and in lieu of the directions in § 141a.1 (d) prepare sample as follows:

Place 5 suppositories in a separatory funnel containing 150 milliliters of peroxide-free ether. Shake the separatory funnel vigorously to bring about complete mixing of the material with the ether. Shake with a 25-milliliter portion of 1 percent phosphate buffer at pH 6.0. Remove the buffer layer and repeat the extraction with three 25-milliliter quantities of buffer. Combine all extracts and make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. The sample may also be prepared as follows: Place 5 suppositories in a glass blending

jar containing 200 milliliters of 1 percent phosphate buffer at pH 6.0. Using a high-speed blender blend for 3 minutes and make the proper estimated dilution in 1 percent phosphate buffer at pH 6.0. The average potency of the suppository is satisfactory if it contains not less than 85 percent of the number of units it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c) using a weighed suppository dissolved in 10 milliliters of dry chloroform and 2 milliliters of methanol from the titrating burette. (Correct for the amount of moisture in the solvents used.)

§ 141a.19 Buffered crystalline penicillin.

Proceed as directed in §§ 141a.1, 141a.2, 141a.3, 141a.4, 141a.5 and 141a.6.

§ 141a.20 Capsules buffered penicillin with pectin hydrolysate.

(a) *Potency.* Proceed as directed in § 141a.1 except paragraph (i) thereof and in lieu of the directions in § 141a.1 (d) prepare samples as follows:

Place the contents of 12 capsules and the empty capsules into a 500-milliliter volumetric flask. Add approximately 200 milliliters of 1 percent phosphate buffer at pH 6.0, shake until the powder has dissolved and the capsules have gelatinized and make to 500 milliliters with the phosphate buffer. Make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. The average potency of capsules buffered penicillin with pectin hydrolysate is satisfactory if it contains not less than 85 percent of the number of units per capsule it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) utilizing the contents of 4 capsules.

§ 141a.21 Capsules penicillin and novobiocin.

(a) *Potency*—(1) *Penicillin content*—(i) *Plate assay.* Proceed as directed in § 141a.1, with the following exceptions:

(*a*) In lieu of the directions prescribed by § 141a.1 (d), prepare the sample by dissolving the contents of a representative number of capsules (usually 5 to 12) in sufficient 1.0-percent potassium phosphate buffer (pH 6.0) to give a stock solution of convenient concentration.

(*b*) In lieu of the directions prescribed by § 141a.1 (e), use as the test organism the novobiocin-resistant strain of Staphylococcus aureus (ATCC 12692). Maintain the organism on agar containing 10 micrograms of novobiocin per milliliter. Prepare an organism suspension by washing the organism from an agar slant (which has been incubated for 24 hours at 32° C.–35° C.) with 3.0 milliliters of sterile physiological saline solution onto a large surface of agar containing 10 micrograms of novobiocin per milliliter. A Roux bottle containing 300 milliliters of agar is satisfactory. Incubate 24 hours at 32° C.–35° C. Wash the resulting growth from the agar surface with sufficient sterile physiological saline solution, so that a tenfold dilution of the bulk suspension will give 20-percent light transmission, using a suitable photoelectric colorimeter with a 650-millimicron filter and an 18-millimeter-diameter test tube as an absorption cell. Run test plates to determine the quantity of bulk suspension (usually 1 milliliter) that should be added to each 100 milliliters of agar to give clear, sharp zones of inhibition of appropriate size.

(ii) *Iodometric assay.* Proceed as directed in § 141a.5 (d) (1), with the following exceptions: Use the contents of a representative number of capsules (usually 5 to 12) dissolved in sufficient 1.0-percent potassium phosphate buffer (pH 6.0) to give a concentration of 2,000 units per milliliter (estimated). In the blank determination add 1 drop of 1.2 *N* HCl to the 2.0-milliliter aliquot of the assay solution immediately before the addition of the 10.0 milliliters of 0.01 *N* iodine. Prepare the inactivated solution as follows: To 5.0 milliliters of the assay solution add 10.0 milliliters of 1 *N* NaOH and allow to stand at room temperature. After 15 minutes add 10.0 milliliters of 1.2 *N* HCl, mix well, and filter through filter paper. To 10.0 milliliters of clear filtrate add 10.0 milliliters of 0.01 *N* iodine.

Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units per capsule that it is represented to contain.

(2) *Novobiocin content.* Proceed as directed in paragraph (c) (1) of this section, except prepare the sample as follows: Place a representative sample (usually 5 to 12 capsules) in a blending jar containing 200 milliliters of 0.1 *M* potassium phosphate buffer (pH 8.0) and blend for 1 minute with a high-speed blender. To an aliquot add sufficient penicillinase to inactivate the penicillin, further dilute with 1-percent potassium phosphate buffer (pH 6.0) to give a final concentration of 0.5 microgram per milliliter (estimated) and allow to stand for ½-hour at 37° C. Its content of novobiocin is satisfactory if it contans not less than 85 percent of the number of milligrams per capsule that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

(c) *Novobiocin used in making the capsules*—(1) *Potency*— (i) *Cylinders (cups).* Use cylinders described in § 141a.1 (a).

(ii) *Culture media.* (*a*) Use the nutrient agar described in § 141a.1 (b) (1) for the seed layer and for carrying the organism.

(*b*) Use the nutrient agar described in § 141a.1 (b) (2) for the base layer.

(iii) *Working standard.* Dissolve a suitable weighed quantity (30 to 50 milligrams) of the working standard (obtained from the Food and Drug Administration) dried as described in § 141a.5(a) in 2 milliliters of ethyl alcohol and then add sufficient 0.1 *M* potassium phosphate buffer (pH 8.0) to give a concentration of 1,000 micrograms per milliliter. This stock solution may be kept for 30 days when stored under refrigeration.

(iv) *Preparation of sample.* Dissolve in sufficient 0.1 *M* potassium phosphate buffer (pH 8.0) to give a convenient stock solution. Further dilute in 1.0-percent potassium phosphate buffer (pH 6.0) to give a final concentration of 0.5 microgram per milliliter (estimated).

(v) *Preparation of test organism.* The test organism is Staphylococcus epidermidis (American Type Culture Collection 12228) which is maintained on slants of agar described under subdivision (ii) (*a*) of this subparagraph. Wash the organism from the agar slant with 3 milliliters of sterile physiological saline solution onto a large agar surface such as that provided by a Roux bottle containing 300 milliliters of the agar described in subdivision (ii) (*a*) of this subparagraph. Spread the suspension of organisms over the entire agar surface with the aid of sterile glass beads. Incubate for 24 hours at 32° C.–35° C., and then wash the resulting growth from the agar surface with sufficient sterile physiological saline solution so that a tenfold dilution of this bulk suspension will give 15-percent light transmission, using a suitable photoelectric colorimeter with a 650-millimicron filter and an 18-millimeter-diameter test tube as an absorption cell. Run test plates to determine the quantity of the bulk suspension (usually 1.5 milliliters) that should be added to each 100 milliliters of agar to give clear, sharp zones of inhibition of appropriate size.

(vi) *Preparation of plates.* Add 21 milliliters of the agar prepared as described in subdivision (ii) (*b*) of this subparagraph to each Petri dish (20 millimeters x 100 millimeters). Distribute the agar evenly in the plates and allow it to harden. Use the plates the same day they are prepared. Melt a sufficient amount of the agar described in subdivision (ii) (*a*) of this subparagraph, cool to 48° C., add the proper amount of the test organism as described above, and mix thoroughly. Add 4 milliliters of this inoculated agar to each Petri dish. Distribute the agar evenly in the plates, cover with porcelain covers glazed on the outside, and allow to harden. After the agar has hardened, place 6 cylinders on the agar surface so that they are at approximately 60° intervals on a 2.8-centimeter radius.

(vii) *Standard curve.* Prepare the daily standard curve by further diluting the 1,000 μg. per milliliter stock solution in 1 percent potassium phosphate buffer (pH 6.0), to obtain concentrations of 0.32, 0.4, 0.5, 0.63, and 0.78 μg. per milliliter. Use three plates for the determination of each point on the curve, except the 0.5 μg. per milliliter concentration, a total of 12 plates. On each of three plates fill three cylinders with the 0.5 μg. per milliliter standard, and fill the other three cylinders with the concentration under test. Thus, there will be thirty-six ½-μg. determinations and nine determinations for each of the other points on the curve. After the plates have incubated, read the diameters of the circles of inhibition. Average the readings of the 0.5 μg. per milliliter concentration and the readings of the point tested for each set of three plates, and average also all 36 readings of the 0.5 μg. per milliliter concentrations. The average of the 36 readings of the 0.5 μg. per milliliter concentration is the correction point for the

curve. Correct the average value obtained for each point to the figure it would be if the 0.5 μg. per milliliter reading for that set of three plates were the same as the correction point. Thus, if in correcting the 0.4 μg. concentration, the average of the 36 readings of the 0.5 μg. concentration is 20.0 millimeters, and the average of the 0.5 μg. concentration of this set of three plates is 19.8 millimeters, the correction is +0.2 millimeter. If the average reading of the 0.4 μg. concentration of these same three plates is 19.0 millimeters, the corrected value is 19.2 millimeters. Plot these corrected values, including the average of the 0.5 μg. per milliliter concentration, on semilog paper, placing the concentration in micrograms per milliliter on the logarithmic scale and the diameter of the zone of inhibition on the arithmetic scale. Draw the standard curve through these points either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e}{5},$$

$$H=\frac{3e+2d+c-a}{5}$$

where

L = corrected zone diameter for the lowest concentration of the standard curve.

H = corrected zone diameter for the highest concentration of the standard curve.

c = average zone diameter of 36 readings of the 0.5 μg. per milliliter standard.

a, b, d, e = corrected average values for the 0.32, 0.4, 0.63, and 0.78 μg. per milliliter standard solutions, respectively.

Plot the values obtained for L and H and connect with a straightline.

(viii) *Assay.* Use 3 plates for each sample. Fill 3 cylinders on each plate with the standard 0.5 microgram per milliliter solution and 3 cylinders with the 0.5 microgram per milliliter (estimated) sample, alternating standard and sample. Incubate all plates, including those containing the standard curve, at 32° C.–35° C. overnight, and measure the diameter of each circle of inhibition. To estimate the potency of the sample, average the zone readings of the standard and the zone readings of the sample on the 3 plates used. If the sample gives a larger zone size than the average of the standard, add the difference between them to the 0.5 microgram per milliliter zone on the standard curve. If the average sample value is lower than the standard value, subtract the difference between them from the 0.5 microgram per milliliter value on the standard curve. From the curve, read the potencies corresponding to these corrected values of zone sizes.

(2) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent, and inject 0.5 milliliter of a solution containing 4 milligrams per milliliter.

(3) *Moisture.* Proceed as directed in § 141a.5 (a).

(4) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution (approximately 25 milligrams per milliliter) of the drug.

(5) *Crystallinity.* Proceed as directed in § 141a.5 (c).

§ 141a.22 Penicillin bougies.

(a) *Potency.* Proceed as directed in § 141a.9(a).

(b) *Moisture.* Proceed as directed in § 141a.7 (c), using 1.0 to 2.0 grams of bougies dissolved in 10 milliliters of dry chloroform if it contains the excipient polyethylene glycol. If it does not contain the excepient polyethylene glycol, proceed as directed in § 141a.5 (a).

§ 141a.23 Crystalline penicillin and epinephrine in oil.

(a) *Potency.* Proceed as directed in § 141a.7(a) except the provisions for warming the sample. When examined by the method described in this section the potency of crystalline penicillin and epinephrine in oil is satisfactory if it is 90 percent or more of the potency represented.

(b) *Sterility.* Proceed as directed in § 141a.7 (b).

(c) *Moisture.* Proceed as directed in § 141a.7 (c).

(d) *Epinephrine content*—(1) *Standard curve.* Prepare a stock standard containing 20 milligrams of U. S. P. epinephrine reference standard in 100 milliliters of phosphate buffer at pH 4.0. This buffer is prepared by adjusting 1 percent phosphate buffer pH 6.0 with 1:100 phosphoric acid (ortho 85 percent) to pH 4.0. The stock standard is stored in the refrigerator and may be used as long as it remains colorless. Transfer 1.0, 2.0, 3.0, 4.0, and 5.0 milliliters of the standard to each of five 100-milliliter volumetric flasks using transfer pipettes. Add 4.0, 3.0, 2.0, and 1.0 milliliters of the phosphate buffer pH 4.0 to the first four flasks respectively to give each a total volume of 5 milliliters. Add 1.0 milliliter of 0.1 *N* iodine to each flask, shake for one minute, add 2.0 milliliters of 0.1 *N* sodium thiosulfate and mix the solution. Make each flask to a volume of 100 milliliters with distilled water. Read the percent light transmission of the colored solutions using a 2.0 centimeter cell and a 490 mμ filter in a suitable photoelectric colorimeter. The instrument is balanced so that the 0.2 mg./100 ml. concentration reads 90 percent light transmission. Prepare a standard curve on semilog paper, plotting the percent light transmission on the logarithmic ordinate scale and the concentration on the abscissa.

(2) *Procedure.* Transfer 1.0 milliliter of the sample with the aid of a hypodermic syringe and needle to a screw-cap test tube (about 30 milliliters capacity), add 5.0 milliliters of U. S. P. chloroform and 10.0 milliliters of 1 percent phosphate buffer pH 6.0 from a transfer pipette. Shake thoroughly for one minute, centrifuge to separate the layers and carefully withdraw a 5.0-milliliter aliquot of the buffer layer using a transfer pipette. Transfer the aliquot to a 50-milliliter volumetric flask, add the calculated amount of 1:100 phosphoric acid to bring the pH to 4.0 (amount to be added previously determined by titration of the 1 percent phosphate buffer pH 6.0 with 1:100 phosphoric acid using a pH meter). Add 1.0 milliliter of 0.1 *N* iodine, shake for one minute, add 2.0 milliliters of 0.1 *N* sodium thiosulfate and mix the solution. Make to a volume of 50 milliliters with distilled water. Set the colorimeter at 90 percent light transmission for the 0.2 milligram/100 milliliters standard as directed above and obtain the percent light transmission of the sample. The concentration obtained directly from the standard curve corresponding to the percent light transmission of the sample × 1.05 equals the concentration of the epinephrine per milliliter of the sample. Crystalline penicillin and epinephrine in oil is satisfactory if it contains not less than 0.24 or more than 0.36 milligram epinephrine per milliliter.

§ 141a.24 Aluminum penicillin.

(a) *Potency.* Proceed as directed in § 141a.1(a), using citrate buffer as prepared in § 141a.16(a) in lieu of phosphate buffer.

(b) *Sterility.* Proceed as directed in § 141a.2.

(c) *Pyrogens.* Proceed as directed in § 141a.3, but in lieu of the directions for preparation of sample in paragraph (b) thereof, prepare sample as follows:

Suspend approximately 60 milligrams in 20 milliliters of pyrogen-free sterile physiological salt solution, adding the salt solution in approximately 1-milliliter aliquots and mixing thoroughly after each addition, utilizing a pyrogen-free glass stirring rod. Centrifuge, warm to 37° C., withdraw the clear supernatant solution, and inject 1 milliliter per kilogram of rabbit.

(d) *Toxicity.* Proceed as directed in § 141a.4, utilizing the solution prepared in paragraph (c) of this section.

(e) *Moisture.* Proceed as directed in § 141a.5 (a).

(f) *pH.* Proceed as directed in § 141a.5 (b), using a saturated solution.

(g) *Penicillin K content.* Proceed as directed in § 141a.5 (f).

§ 141a.25 Aluminum penicillin in oil.

(a) *Potency, sterility.* Proceed as directed in § 141a.7.

(b) *Moisture.* Proceed as directed in § 141a.23 (c).

§ 141a.26 Procaine penicillin.

(a) *Potency.* Proceed as directed in § 141a.1, or by the iodometric method as described in § 141a.5(d)(1), except prepare the sample as follows: Dissolve a weighed sample (approximately 50 milligrams) in 2.0 milliliters of redistilled methanol. Further dilute this solution with sufficient 1 percent phosphate buffer pH 6.0 to give a concentration of 2.0 milligrams per milliliter.

(b) *Sterility.* Proceed as directed in § 141a.2.

(c) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent.

(d) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent, and inject 0.5 milliliter of a solution containing 2,000 units per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.7 (c), but in lieu of the directions for preparing the sample in subparagraph (3) thereof prepare the sample and calculate as follows: Accurately weigh about 300 milligrams of the sample into a dry titrating vessel, add an

excess of the Karl Fischer reagent and back titrate with water-methanol solution until the endpoint is reached.

$$\text{Percent moisture} = \frac{(a_1 - a_2 f) \times e \times 100}{W_s}$$

where W_s = weight of sample in milligrams.

(f) *pH.* Proceed as directed in § 141a.5 (b) using a saturated aqueous solution prepared by adding 300 milligrams per milliliter.

(g) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(h) *Penicillin G content.* Proceed as directed in § 141a.5 (e) using the following formula for calculating the percent of procaine penicillin G:

$$\text{Percent of procaine penicillin G} = \frac{\text{N-ethyl piperidine penicillin precipitate} \times 263.1}{\text{Weight of sample in milligrams}}$$

and in lieu of the first four sentences in § 141a.5 (e) (2) proceed as follows:

Accurately weigh approximately 100 milligrams of the sample to be tested in a glass test tube or glass vial of approximately 10-milliliter capacity. Add 2 milliliters of water and cool to 0° C. to 5° C. Add 2 milliliters of the amyl acetate solution and 0.5 milliliter of the phosphoric acid solution, stopper and shake vigorously for aproximately 15 seconds. Add a second 0.5-milliliter portion of the phosphoric acid solution and shake vigorously again. Centrifuge to obtain a clear separation of the two layers (approximately 20 seconds). If any procaine penicillin remains undissolved, add a third portion of 0.5 milliliter of the phosphoric acid solution and repeat the shaking and centrifugation.

(i) *Penicillin K content.* Weigh from 30–35 milligrams of the sample to be tested in a glass test tube or glass vial of approximately 10-milliliter capacity. Add 2.0 milliliters of chloroform U. S. P. and cool the mixture to 0° C.–5° C. in an ice bath. Add 1.0 milliliter of cold 1–4 phosphoric acid solution, stopper and shake vigorously for 15 seconds. Centrifuge to obtain a clear separation of the layers (approximately 20 seconds). After centrifuging, remove 1.0 milliliter of the chloroform layer with a pipette or syringe equipped with a suitable needle. Immediately place the 1.0 milliliter of chloroform in a 125-milliliter separatory funnel containing 29.0 milliliters of chloroform and 15.0 milliliters of 0.3 *M* phosphate (Na_2HPO_4 and KH_2PO_4) buffer pH 6.0 at room temperature and shake for 1 minute. Allow the mixture to stand with occasional swirling to settle the droplets of chloroform until the top layer is clear (usually about 10 minutes). Draw off all but about 2 milliliters of the lower chloroform layer through a small pledget of cotton into a glass-stoppered flask. Take a 4.0-milliliter aliquot of the buffer solution remaining in the separatory funnel and a 10.0-milliliter aliquot of the chloroform solution and determine the milligrams per milliliter of penicillin in each by the iodometric assay procedure described in § 141a.5 (d) (1) using 4.0 milliliters of the 1 *N* NaOH and 4.0 milliliters of the 1.2 *N* HCl for the two above aliquots. Make blank determinations on the same size aliquots. Calculate the percent penicillin in the buffer layer on the basis that the sum of the penicillin found in the buffer layer and in the chloroform layer is 100 percent. The percent penicillin K = (98.46 − percent found in buffer) × 3.34.

§ 141a.27 Procaine penicillin in oil.

(a) *Potency.* Proceed as directed in § 141a.1, except § 141a.1(i) and in lieu of the directions in § 141a.1(d), prepare the sample by one of the following methods:

(1) *Bioassay*—(i) *Chloroform-alcohol solution.* By means of a 2-milliliter hypodermic syringe, introduce 1 milliliter of the well shaken sample into a 50-milliliter volumetric flask. Add 3 milliliters to 4 milliliters of chloroform, shake the flask thoroughly, and make to 50 milliliters with absolute alcohol. Mix thoroughly, withdraw a 1-milliliter aliquot and make the proper estimated dilutions in 1 percent phosphate buffer, pH 6.0.

(ii) *Blending.* Introduce 1 milliliter of the well shaken sample by means of a 2.0-milliliter hypodermic syringe into a blending jar containing 98 milliliters of 1 percent phosphate buffer, pH 6.0, and 1 milliliter of polysorbate 80. Using a high-speed blender, blend the mixture for 1 minute and make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0.

(2) *Iodometric chemical assay*—(i) *Chloroform-alcohol solution.* Introduce a representative quantity (usually 1 milliliter) of the well shaken sample into a flask and dissolve in sufficient chloroform-absolute ethanol (1+1) solvent to give a concentration of 2,000 units to 8,000 units per milliliter. An aliquot of this solution containing 2,000 units (estimated) is used as the solution for assay.

(ii) *Extraction.* Accurately measure two representative portions of the sample (usually 1 milliliter) each equivalent to from 100,000 units to 300,000 units (estimated). Place one portion in a centrifuge tube containing 10 milliliters of chloroform and 10.0 milliliters of 1 percent phosphate buffer, pH 6.0. Shake the tube for 1 minute and centrifuge to obtain a substantially clear buffer layer. Dilute 5.0 milliliters of the buffer layer with sufficient 1 percent phosphate buffer, pH 6.0, to give a concentration of about 2,000 units per milliliter, and mix. Use 2.0 milliliters of this solution as the blank. Place the second portion of the sample in a centrifuge tube containing 10 milliliters of chloroform and 10.0 milliliters of 1 *N* NaOH. Shake the tube for 1 minute and allow to stand for 15 minutes. Shake the tube again and centrifuge to obtain a substantially clear NaOH layer.[1] Dilute 5.0 milliliters of the NaOH layer with sufficient 1 *N* NaOH to give a concentration of about 2,000 units per milliliter. Use 2.0 milliliters of this solution as the inactivated solution. From the titration data calculate the amount of penicillin in the sample. If the label represents the potency of the procain penicillin in oil as 100,000 units per milliliter, it is satisfactory if it is 85 percent or more of the potency so represented; if represented as 300,000 units per milliliter, it is satisfactory if it is 90 percent or more of the potency so represented.

§ 141a.28 Crystalline penicillin for inhalation therapy.

(a) *Potency.* Proceed as directed in § 141a.1, or by the iodometric method as described in § 141a.5(d) (1).

(b) *Moisture.* Proceed as directed in § 141a.5 (a), except if it is procaine penicillin proceed as directed in § 141a.26 (e).

§ 141a.29 Procaine penicillin for aqueous injection.

(a) *Potency.* Using as the sample for assay a representative aliquot of the suspension equivalent to one dose (or, if it is a dry mixture of the drug, a representative aliquot of the drug equivalent to one dose after it has been reconstituted as directed in the labeling), proceed as directed in § 141a.1, using approximately 50 to 100 milliliters of redistilled methyl alcohol, dimethyl formamide, or formamide to dissolve the sample, or by the iodometric method as described in § 141a.5(d) (1), except dissolve the sample in about 5.0 milliliters of redistilled methyl alcohol, dimethyl formamide, or formamide prior to diluting with 1 percent phosphate buffer, pH 6.0. Its potency is satisfactory if it contains not less than 90 percent of the number of units that it is represented to contain.

(b) *Sterility.* Use the entire contents of single-dose containers or the equivalent of approximately 300 milligrams (activity) from each multiple-dose container, and proceed as directed in § 141a.2, except if it is the aqueous suspension of the drug and does not contain a preservative, incubate all tubes for 14 days.

(c) *Moisture.* Proceed as directed in § 141a.26 (e).

(d) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent.

(e) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent, and inject 0.25 milliliter of a solution containing 4,000 units per milliliter.

(f) *pH*—(1) *Dry mixture of the drug.* Proceed as directed in § 141a.5 (b), using the solution or suspension resulting when the amount of diluent recommended in the labeling is added.

(2) *Aqueous suspension of the drug.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension.

§ 141a.30 Ephedrine penicillin.

(a) *Potency.* Proceed as directed in § 141a.1, or by the iodometric method as described in § 141a.5(d) (1), except dilute the sample with sufficient 1 percent phos-

phate buffer pH 6.0 to give a concentration of 2.0 milligrams per milliliter.

(b) *Sterility.* Proceed as directed in § 141a.2.

(c) *Pyrogens.* Proceed as directed in § 141a.3.

(d) *Toxicity.* Proceed as directed in § 141a.4.

(e) *Moisture.* Proceed as directed in § 141a.5 (a).

(f) *pH.* Proceed as directed in § 141a.5 (b).

(g) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(h) *Penicillin G content.* Proceed as directed in § 141a.5 (e) using an accurately weighed sample of approximately 80 mg. and the following formula for calculating the percent of ephedrine penicillin G:

$$\text{Percent of ephedrine penicillin G} = \frac{\text{Milligrams } N\text{-ethyl piperidine penicillin precipitate} \times 223.2}{\text{Weight of sample in milligrams}}$$

(i) *Penicillin K content.* Proceed as directed in § 141a.5 (f).

§ 141a.31 Ephedrine penicillin tablets.

(a) *Potency.* Proceed as directed in § 141a.9 (a) or by the iodometric method as described in § 141a.5 (d) (1), using 6 tablets dissolved in sufficient 1 percent phosphate buffer pH 6.0 to give a concentration of 2,000 units per milliliter.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.32 Procaine penicillin and buffered crystalline penicillin for aqueous injection.

(a) *Total potency (except in single-dose container), sterility, moisture, pyrogens, toxicity, pH.* Proceed as directed in § 141a.29.

(b) *Buffered crystalline penicillin content*—(1) *Preparation of the solution for assay.* Add the indicated amount of distilled water to the contents of a vial of the sample, and shake well. Withdraw one dose of the suspension with a hypodermic syringe and place in a 10-milliliter volumetric flask. Add 20-percent sodium sulfate solution almost to the mark, centrifuge sufficiently to see the meniscus, make to volume with 20-percent sodium sulfate solution, shake well, and centrifuge to obtain a clear or reasonably clear solution. Dilute a 5.0-milliliter aliquot of this clear solution with 1-percent phosphate buffer, pH 6.0, to give a solution for assay of approximately 2,000 units per milliliter.

(2) *Iodometric assay for total penicillin in the solution for assay.* Determine the quantity of penicillin in the solution for assay by the iodometric assay procedure described in § 141a.5 (d) (1).

(3) *Colorimetric determination of procaine penicillin in the solution for assay.* Transfer an aliquot of the solution for assay to a 50-milliliter volumetric flask. Determine the quantity of procaine penicillin in this solution by the following method:

(i) *Reagents*—(a) *Sodium nitrite solution.* Dissolve 0.1 gram of sodium nitrite in 100 milliliters of distilled water. Prepare fresh solution every week and store under refrigeration.

(b) *Ammonium sulfamate solution.* Dissolve 0.5 gram of ammonium sulfamate in 100 milliliters of distilled water and store under refrigeration.

(c) *N-(1-naphthyl)-ethylenediamine solution.* Dissolve 0.1 gram of *N*-(1-naphthyl)-ethylenediamine dihydrochloride in 100 milliliters of distilled water. Prepare fresh solutions every week and store under refrigeration.

(d) *Standard procaine solution.* Prepare a standard solution containing 27.55 milligrams of procaine hydrochloride U. S. P. in a liter of distilled water (each milliliter of the standard solution is equivalent to 60 units of procaine penicillin).

(ii) *Standards.* Transfer, respectively, 1.0, 2.0, 3.0, 4.0, and 5.0 milliliters of the standard solution and 5.0 milliliters of distilled water to each of six 50-milliliter volumetric flasks. Add 4.0, 3.0, 2.0, and 1.0 milliliters of water to the first four flasks, respectively, to give each a volume of 5.0 milliliters.

(iii) *Procedure.* To each flask of the standards and the solution for assay add 0.5 milliliter of 4 *N* HCl, 1.0 milliliter of the sodium nitrite solution, 1.0 milliliter of the ammonium sulfamate, and 1.0 milliliter of the *N*-(1-naphthyl)-ethylenediamine solution. Mix and wait two minutes after each addition. Make each flask to volume of 50 milliliters with distilled water. Determine the absorbency of the colored solutions at 550 mμ in a suitable photo electric colorimeter. The instrument is balanced so that the zero concentration reads zero absorbancy. Plot the standard curve on coordinate graph paper. Obtain the procaine penicillin content of the solution for assay directly from the point on the standard curve corresponding to its absorbancy.

(4) The content of buffered crystalline penicillin in one dose of the product is calculated as follows:

$$A = (B - C)F,$$

where

A = buffered crystalline penicillin content of the product.

B = total number of units of penicillin per milliliter as determined in subparagraph (2) of this paragraph.

C = number of units of procaine penicillin per milliliter as determined in subparagraph (3) of this paragraph.

F = appropriate dilution factor depending on the dilution made in the preparation of the solution for assay.

The content of buffered crystalline penicillin in the batch is satisfactory when determined by the method described in this paragraph if it is not less than 85 percent of that which it is represented to contain.

(c) *Procaine penicillin.* The procaine penicillin content of the batch is the difference between the total potency determined by the method described in paragraph (a) or (d) of this section and the content of the buffered crystalline penicillin determined by the method described in paragraph (b) of this section. The procaine penicillin content of the batch is satisfactory when determined by the method described in this paragraph if it is not less than 85 percent of that which it is represented to contain.

(d) *Total potency of a one-dose container.* Wash out the material remaining in the 10-milliliter volumetric flask referred to in paragraph (b) (1) of this section with 1-percent phosphate buffer, pH 6.0. Dilute to give a concentration of approximately 2,000 units per milliliter, and assay by the iodometric method described in § 141a.5 (d) (1). Obtain the total potency by adding the number of units found in this solution (units per milliliter × volume) to the number of units found (units per milliliter × volume) in the solution assayed in accordance with paragraph (b) (2) of this section.

§ 141a.33 Buffered penicillin powder.

(a) *Potency.* Reconstitute the drug as directed in its labeling and proceed as directed in § 141a.1, except if it is procaine penicillin proceed as directed in § 141a.48(a). Its potency is satisfactory if it contains not less than 90 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.26(e).

§ 141a.34 Procaine penicillin and crystalline penicillin in oil.

(a) *Total potency.* Proceed as directed in § 141a.27(a).

(b) *Crystalline penicillin.* Proceed as directed in § 141a.32(b), except prepare the sample as follows: Introduce a representative quantity of the well shaken sample (usually 1 milliliter) into a 30-milliliter centrifuge tube equipped with a screw cap. Add 10.0 milliliters of chloroform and 10.0 milliliters of a 20 percent sodium sulfate solution, shake well for about 1 minute, and centrifuge to obtain a clear upper layer.

(c) *Procaine penicillin.* The difference between the total penicillin as determined by paragraph (a) of this section and the crystalline penicillin as determined by paragraph (b) of this section represents the amount of procaine penicillin present.

(d) The procaine penicillin and the crystalline penicillin content of the batch are satisfactory when assayed by the methods described in this section if each is not less than 85 percent of that which it is represented to contain.

(e) *Sterility.* Proceed as directed in § 141a.7 (b), except in the case of multiple-dose containers use approximately 400 milligrams (activity) from each container, in lieu of 300 milligrams.

(f) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.35 Penicillin-streptomycin ointment; penicillin-dihydrostreptomycin ointment.

(a) *Potency*—(1) *Total penicillin content.* Proceed as directed in § 141a.8(a) or § 141a.5(d)(1), except that if the iodometric chemical assay described in § 141a.5(d)(1) is used prepare the sample as follows: Accurately measure two representative portions of the sample, each equivalent to about 20,000 units. Place one portion in a centrifuge

tube containing 10.0 milliliters of 1 percent phosphate buffer, pH 6.0, and 10.0 milliliters of chloroform for each 5 milliliters or grams of sample. Shake the tube for 1 minute and centrifuge to obtain a substantially clear buffer layer. Use 2.0 milliliters of this solution as the blank. Add one drop of 1.2 *N* HCl to the blank immediately before the addition of the 10.0 milliliters of 0.01 *N* I_2. Immediately titrate with 0.01 *N* $Na_2S_2O_3$. Place the second portion of the sample in a centrifuge tube containing 10.0 milliliters of 1 *N* $NaHCO_3$ (previously adjusted to a pH of 9.3±0.2 with 1.0 *N* NaOH) and 10.0 milliliters of chloroform for each 5 milliliters or grams of sample. Shake the tube for 1 minute and centrifuge to obtain a substantially clear aqueous layer. To 2.0 milliliters of the aqueous layer, add 2.0 milliliters of 1 *N* NaOH and allow to stand for 15 minutes. Add sufficient 1.2 *N* HCl to obtain a pH of 1.0, then add 10.0 milliliters of 0.01 *N* I_2. Allow to stand for 15 minutes and then titrate with 0.01 *N* $Na_2S_2O_3$. From the titration data calculate the amount of penicillin in the sample. Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Crystalline sodium penicillin or potassium penicillin content*—(i) *Direct method*—(*a*) *Preparation of the solution for assay.* Accurately measure a representative portion of the sample equivalent to about 20,000 units of crystalline sodium penicillin or potassium penicillin and place it in a centrifuge tube containing 10.0 milliliters of 20 percent sodium sulfate solution and 10.0 milliliters of chloroform for each 5 milliliters or grams of sample. Shake the tube for 1 minute and then centrifuge to obtain a substantially clear aqueous layer. This is used as the solution for assay.

(*b*) *Iodometric assay for total penicillin in the solution for assay.* Determine the quantity of penicillin in the solution for assay by the iodometric assay procedure described in § 141a.5(d)(1).

(*c*) *Colorimetric determination of procaine penicillin in the solution for assay.* (*1*) If the sample does not contain sulfonamides, determine the procaine penicillin in the solution for assay by the colorimetric procedure described in § 141a.32(b)(3).

(*2*) If the sample contains sulfonamides, proceed as follows: Place 10.0 milliliters of the solution for assay in a separatory funnel containing 2 milliliters of 1 *N* NaOH and 10.0 milliliters of chloroform and shake for 1 minute. Allow the layers to separate and collect the lower chloroform layer in a cylinder containing 10.0 milliliters of 4 *N* HCl. Shake for 1 minute and allow the layers to separate. Using the upper acid layer as the solution for assay, determine the procaine penicillin content by the colorimetric procedure described in § 141a.32(b)(3).

(*d*) The content of crystalline sodium or potassium penicillin in the sample is calculated as follows:

$$A=(B-C)F,$$

Where:

A = crystalline sodium penicillin or potassium penicillin content of the sample.

B = total number of units of penicillin per milliliter as determined in subdivision (i)(*b*) of this subparagraph.

C = number of units of procaine penicillin per milliliter as determined in subdivision (i)(*c*) of this subparagraph.

F = appropriate dilution factor depending on the dilution made in the preparation of the solution for assay and the size of the representative portion of the sample tested.

(ii) *Indirect method.* The content of crystalline sodium or potassium penicillin is the difference between the total penicillin content determined in subparagraph (1) of this paragraph and the procaine penicillin determined in subparagraph (3)(i) of this paragraph. Its content of crystalline sodium penicillin or potassium penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(3) *Procaine penicillin content*—(i) *Direct method.* Using the stock solution prepared for bioassay in subparagraph (1) of this paragraph, determine the procaine penicillin content colorimetrically as directed in subparagraph (2)(i)(*c*)(2) of this paragraph.

(ii) *Indirect method.* The procaine penicillin content of the sample is the difference between the total penicillin content determined in subparagraph (1) of this paragraph and the crystalline sodium penicillin or potassium penicillin content determined in subparagraph (2) of this paragraph. Its content of procaine penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(4) *Streptomycin content.* Proceed as directed in § 141b.101 of this chapter, except paragraph (k) of that section, and in lieu of the directions in § 141b.101 (e) and (j)(3), test a representative portion of the sample (usually approximately 1 gram, accurately weighed) or the entire contents of a single-dose container prepared by one of the following methods:

(i) *To assay by the cup-plate method.* Use either extraction or blending.

(*a*) *Extraction.* Place the sample in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. If the sample consists of substantially more than 1 gram, use 100 milliliters of ether. Shake the sample and ether until homogeneous. Add 20 milliliters of 0.1 *M* potassium phosphate buffer, pH 8.0, and shake. If the sample consists of substantially more than 1 gram, use 50 milliliters of buffer. Allow the layers to separate. Remove the buffer layer and repeat the extraction with new portions of buffer at least three times and any additional times necessary to ensure complete extraction of the antibiotic. Combine the extractives and make up to an appropriate measured volume with buffer. To a suitable aliquot add sufficient penicillinase and let stand for 30 minutes at 37° C. to inactivate the penicillin. After inactivation, make the proper estimated dilution with buffer at pH 8.0.

(*b*) *Blending.* Place the sample in a blending jar containing 1.0 milliliter of 10-percent aqueous solution of polysorbate 80 and sufficient 0.1 *M* potassium phosphate buffer, pH 8.0, to give a final volume of 500 milliliters. Using a high-speed blender, blend the mixture for 3 minutes. To a suitable aliquot, add sufficient penicillinase and let stand for 30 minutes at 37° C. to inactivate the penicillin. After inactivation, make the proper estimated dilutions with buffer at pH 8.0.

(ii) *To assay by the turbidimetric method.* Place the sample in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. If the sample consists of substantially more than 1 gram, use 100 milliliters of ether. Shake the sample and ether until homogeneous. Add 20 milliliters of distilled water, and shake. If the sample consists of substantially more than 1 gram, use 50 milliliters of water. Allow the layers to separate. Remove the aqueous layer and repeat the extraction with new portions of water at least three times and any additional times necessary to ensure complete extraction of the antibiotic. Combine the extractives, and make to an appropriate measured volume with water. Remove the aliquot and, if the ratio of the content of penicillin to the content of streptomycin is equal to or greater than one unit for each microgram, add sufficient penicillinase and let stand for 30 minutes at 37° C. to inactivate the penicillin. Make the proper estimated dilutions with distilled water. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(5) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (4) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b).

§ 141a.36 Penicillin-streptomycin bougies; penicillin-dihydrostreptomycin bougies.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.9(a), except the last sentence of that paragraph. Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Using 12 bougies, proceed as directed in § 141b.101 of this chapter, except paragraph (k) of that section, and if the cup-plate method is used, use potassium phosphate buffer (pH 7.8–8.0) for dissolving the sample in lieu of sterile distilled water as directed in § 141b.101 (e) of this chapter and add sufficient penicillinase to the solution under test to completely inactivate the penicillin present. If the turbidimetric method is used, inactivation with penicillinase is not necessary unless the ratio of the content of penicillin to the content of streptomycin is equal to or greater than 1.0 unit for each microgram. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (2) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.22 (b).

§ 141a.37 Penicillin-bacitracin ointment.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.8(a), except the last sentence of that paragraph. Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units it is represented to contain.

(2) *Bacitracin content.* Proceed as directed in § 141e.402 (a) of this chapter, except that sufficient penicillinase is added to the sample under test to completely inactivate the penicillin present. Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b).

§ 141a.38 Procaine penicillin and streptomycin in oil; procaine penicillin and dihydrostreptomycin in oil.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.35(a) or § 141a.27(a)(1)(i). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141a.35(a)(4). Its content of streptomycin satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in § 141a.35(a)(5). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(b) *Moisture.* Using 1 milliliter as the test sample proceed as directed in § 141a.7 (c).

§ 141a.39 Penicillin-streptomycin; penicillin-dihydrostreptomycin veterinary.

(a) *Potency*—(1) *Sodium or potassium penicillin content.* Proceed as directed in § 141a.32(b), except prepare the sample as follows: Add the indicated amount of distilled water to the contents of a vial of the sample and shake well. Withdraw one dose of the suspension or solution with a hypodermic syringe and place in a 10-milliliter volumetric flask. Also, with the further exception that in the iodometric assay, one drop of 1.2 *N* HCl is added to the blank immediately before the addition of the 0.01 *N* I_2. The sodium or potassium penicillin content is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(2) *Total penicillin content.* Proceed as directed in § 141a.1, except paragraphs (d) and (i) of that section. In lieu of the directions in § 141a.1(d), place a representative aliquot of the sample in a blending jar, add 1.0 milliliter of polysorbate 80 and sufficient 1 percent phosphate buffer, pH 6.0, to make a total volume of 500 milliliters. Blend 3 to 5 minutes. For the alternative iodometric test, proceed as directed in § 141a.5(d)(1), except add one drop of 1.2 *N* HCL to the blank immediately before the addition of the 0.01 *N* I_2.

(3) *Procaine penicillin content.* Proceed as directed in § 141a.32 (c). The procaine penicillin content is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(4) *l-Ephenamine penicillin G content.* Proceed as directed in § 141a.43 (a), except that in the iodometric assay one drop of 1.2 *N HCl* is added to the blank immediately before the addition of the 0.01 *N* I_2. The *l*-ephenamine penicillin G content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(5) *Diethylaminoethyl ester penicillin G hydriodide content.* Proceed as directed in § 141a.51 (a), except that in the iodometric assay one drop of 1.2 *N* HCl is added to the blank immediately before the addition of the 0.01 *N* I_2. The diethylaminoethyl ester penicillin G hydriodide content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(6) *Streptomycin content.* Proceed as directed in § 141b.101 (j) and (k) of this chapter.

(7) *Dihydrostreptomycin content.* Proceed as directed in § 141b.108 (a) of this chapter.

(b) *Sterility.* Use the entire contents of single-dose containers or the equivalent of approximately 0.5 gram (combined activity) for each multiple-dose container, and proceed as directed in § 141a.2, except that no control tube is used in the test for bacteria.

(c) *Toxicity.* Proceed as directed in § 141a.4, using as a test dose 0.5 milliliter of a solution of the sample containing 1.0 milligram of streptomycin or dihydrostreptomycin per milliliter.

(d) *Pyrogens.* Proceed as directed in § 141a.3, using as a test dose 2 milliliters per kilogram of a solution containing 5 milligrams of streptomycin or dihydrostreptomycin per milliliter.

(e) *Moisture.* Proceed as directed in §141a.5(a), except that if procaine penicillin is used proceed as directed in § 141a.26(e).

(f) *pH.* Proceed as directed in § 141a.5 (b), using the solution or suspension resulting when the amount of diluent recommended in the labeling is added.

§ 141a.40 Penicillin tooth powder.

(a) *Potency.* Proceed as directed in § 141a.1.

(b) *Moisture.* Proceed as directed in § 141a.7 (c), but in lieu of the directions for preparing the sample in subparagraph (3) thereof prepare the sample and calculate as follows: Accurately weigh about 1 gm. of the sample into a dry titrating vessel. Add an excess of the Karl Fischer reagent and back titrate immediately with water-methanol solution until the end point is reached. (The entire operation from the addition of the Karl Fischer reagent until the end point is reached should not exceed 1 minute.)

$$\text{Percent moisture} = \frac{(V_s - V_s f) \times e \times 100}{W_s},$$

where W_s = weight of sample in milligrams.

§ 141a.41 Penicillin-bacitracin troches; penicillin-zinc bacitracin troches.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.12 (a). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units per troche that it is represented to contain.

(2) *Bacitracin or zinc bacitracin content.* Proceed as directed in § 141e.404 (a) of this chapter, except that sufficient penicillinase is added to the solution under test to completely inactivate the penicillin present. Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units per troche that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.42 Crystalline penicillin and bacitracin.

(a) *Potency*—(1) *Content of penicillin.* Proceed as directed in § 141a.1. Its content of penicillin is satisfactory if it contains not less than 90 percent of the number of units it is represented to contain.

(2) *Content of bacitracin.* Proceed as directed in § 141e.401 (a) of this chapter, except that sufficient penicillinase is added to the sample under test to completely inactivate the penicillin present. Its content of bacitracin is satisfactory if it contains not less than 85 percent and not more than 115 percent of the number of units it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.39 (b).

(c) *Toxicity.* Proceed as directed in § 141a.4 except use physiological salt solution as the diluent.

(d) *Pyrogens.* Proceed as directed in § 141a.3 using as a test dose 1.0 milliliter per kilogram of a solution containing 300 units of bacitracin per milliliter. Use physiological salt solution as the diluent.

(e) *Moisture.* Proceed as directed in § 141a.5 (a).

(f) *pH.* Proceed as directed in § 141a.5 (b), using a solution prepared as directed in the labeling for the drug.

§ 141a.43 *l*-Ephenamine penicillin G.

(a) *Potency.* Proceed as directed in § 141a.1, except in lieu of § 141a.1(d) dissolve the sample in sufficient redistilled methanol to give a concentration of 5,000 units to 10,000 units per milliliter and then dilute with sufficient 1 percent phosphate buffer, pH 6.0, to give an appropriate stock solution.

(b) *Sterility.* Proceed as directed in § 141a.2.

(c) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent and inject 2 milliliters per kilogram of a solution containing 800 units per milliliter.

(d) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent and inject, in a 10-second interval, 1.0 milliliter of a solution containing 800 units per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.5 (a).

(f) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution prepared by adding 300 milligrams per milliliter.

(g) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(h) *Heat stability.* Proceed as directed in § 141a.5 (d) (1), except prepare the sample as follows: Dissolve the sample in 5 milliliters of redistilled methanol. Further dilute this solution with sufficient 1-percent phosphate buffer pH 6.0 to give a concentration of 2.0 milligrams per milliliter.

(i) *Penicillin G content.* Proceed as directed in § 141a.26 (h) using the following formula for calculating the percent of *l*-ephenamine penicillin G:

$$\text{Percent of } l\text{-ephenamine penicillin G} = \frac{N\text{-ethyl piperidine penicillin precipitate} \times 251}{\text{Weight of sample in milligrams}}$$

(j) *Specific rotation.* Accurately weigh approximately 125 milligrams of the sample in a 25-milliliter glass-stoppered volumetric flask and dissolve in about 15 milliliters of water-acetone (1+1) at 20° C. Dilute to 25 milliliters with water-acetone (1+1) at 20° C. and mix thoroughly. Transfer the solution to a 200-millimeter tube, determine the angular rotation in a suitable polarimeter, using sodium light or a 5,893 Angstrom filter, and calculate the specific rotation. The determination must be completed within ½ hour from the time the solution is prepared.

§ 141a.44 *l*-Ephenamine penicillin G in oil.

(a) *Potency.* Proceed as directed in § 141a.27(a), except the last sentence thereof. If it is represented to contain less than 300,000 units per milliliter, its potency is satisfactory if it contains not less than 85 percent of the number of units so represented. If it is represented to contain 300,000 units per milliliter, its potency is satisfactory if it contains not less than 90 percent of the number of units so represented.

(b) *Sterility.* Proceed as directed in § 141a.7 (b).

(c) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.45 *l*-Ephenamine penicillin G for aqueous injection.

(a) *Potency.* Proceed as directed in § 141a.43(a), using as the sample for assay a representative aliquot of the suspension equivalent to one dose; or if it is a dry mixture of the drug, a representative aliquot of the drug equivalent to one dose after it has been reconstituted as directed in the labeling. Its potency is satisfactory if it contains not less than 90 percent of the number of units that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.2, except that prior to sterilization add 0.5 milliliter of polysorbate 80 to each tube of thioglycolate and Sabouraud medium. After sterilization, add sufficient penicillinase to each tube of Sabouraud medium to completely inactivate the penicillin used in the test. During the period of incubation, shake the tubes once daily until solubilization is achieved.

(c) *Moisture.* Proceed as directed in §141a.5 (a).

(d) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent and inject 2 milliliters per kilogram of a solution containing 800 units per milliliter.

(e) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent and inject, in a 10-second interval, 1.0 milliliter of a solution containing 800 units per milliliter.

(f) *pH*—(1) *Dry mixture of the drug.* Proceed as directed in § 141a.5(b), using the suspension resulting when the product is reconstituted as directed in the labeling.

(2) *Aqueous suspension of the drug.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension.

§ 141a.46 Procaine penicillin in streptomycin sulfate solution; procaine penicillin in dihydrostreptomycin sulfate solution veterinary.

(a) *Potency*—(1) *Procaine penicillin content.* Proceed as directed in § 141a.1, except paragraphs (d) and (i) of that section. In lieu of the directions in § 141a.46(d), place a representative aliquot of the sample in a blending jar, add 1.0 milliliter of polysorbate 80 and sufficient 1 percent phosphate buffer, pH 6.0, to make a total volume of 500 milliliters. Blend 3 to 5 minutes. If the iodometric assay is used, 1 drop of the 1.2 *N* HCl is added to the blank immediately before the addition of the 0.01 *N* I_2. Its content of procaine penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin sulfate content.* Proceed as directed in § 141b.101 (j) and (k) of this chapter.

(3) *Dihydrostreptomycin sulfate content.* Proceed as directed in § 141b.108 (a) of this chapter.

(b) *Sterility.* Proceed as directed in § 141a.39 (b).

(c) *Toxicity.* Proceed as directed in § 141a.4, using as a test dose 0.5 milliliter of a solution of the sample containing 1.0 milligram of streptomycin or dihydrostreptomycin per milliliter.

(d) *Pyrogens.* Proceed as directed in § 141a.39 (d).

(e) *pH.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension.

§ 141a.47 Benzathine penicillin G.

(a) *Potency.* Proceed as directed in § 141a.1, except if the bioassay method is used dissolve the sample to be tested in sufficient dimethyl formamide, formamide or redistilled methanol prior to diluting with phosphate buffer solution. If the iodometric method is used proceed as directed in § 141a.5(d), except in preparing the blank solution weigh 30–60 milligrams of the sample and make a suspension of 2 milligrams per milliliter in 1-percent phosphate buffer at pH 6.0. Shake well, pipette 2.0 milliliters into a 125-milliliter glass-stoppered Erlenmeyer flask, add 10 milliliters 0.01 *N* iodine and immediately titrate with 0.01 *N* $Na_2S_2O_3$. In preparing the solution for inactivation dissolve a weighed sample (30–60 milligrams) in sufficient 1 *N* NaOH to give 2.0 milligrams per milliliter. Pipette a 2.0-milliliter aliquot into a 125-milliliter glass-stoppered Erlenmeyer flask, and after 15 minutes add 2.0 milliliters 1.2 *N* HCl and 10 milliliters 0.01 *N* iodine. Allow to stand for 15 minutes and titrate the excess iodine with 0.01 *N* $Na_2S_2O_3$.

(b) *Sterility.* Proceed as directed in § 141a.2, except prior to sterilization add 0.5 milliliter of polysorbate 80 to each tube of thioglycolate and Sabouraud's medium, and after sterilization add sufficient penicillinase to each tube of Sabouraud's medium to completely inactivate the penicillin used in the test. During the period of incubation, shake the tubes at least once daily.

(c) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent and inject 0.25 milliliter of a suspension containing 4,000 units per milliliter.

(d) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent and inject 0.5 milliliter per kilogram of rabbit of a suspension containing 4,000 units per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.26 (e).

(f) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution prepared by adding 5 milligrams per milliliter.

(g) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(h) *Penicillin G content.* Dissolve 50 milligrams of the sample, accurately weighed, in absolute methyl alcohol and make to a volume of 100 milliliters with absolute methyl alcohol. Using a suitable spectrophotometer, determine the absorbance of the solution in a 1-centimeter cell at 263 mμ compared with absolute methyl alcohol as a blank.

$$\text{Percent benzathine penicillin G} = \frac{\text{Absorbance at 263 m}\mu \times 100{,}000}{\text{Milligrams of sample (per 100 milliliters)} \times a_{bs}},$$

where:

a_{bs} = absorptivity (1%, 1 cm.) of benzathine penicillin G working standard, similarly treated.

§ 141a.48 Benzathine penicillin G oral suspension, benzathine penicillin G for oral suspension.

(a) *Potency.* Proceed as directed in § 141a.47(a), using as the sample for assay a representative aliquot of the oral suspension; or if it is a dry mixture of the drug, a representative aliquot of the drug, reconstituted as directed in the labeling. Its potency is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *pH.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension or the suspension pre-

pared as directed in the labeling of the drug.

(c) *Moisture (if it is a dry mixture of the drug).* Proceed as directed in § 141a.26 (c).

§ 141a.49 Penicillin-streptomycin-bacitracin ointment; penicillin-dihydrostreptomycin-bacitracin ointment; penicillin-streptomycin-bacitracin methylene disalicylate ointment; penicillin-dihydrostreptomycin-bacitracin methylene disalicylate ointment.

(a) *Potency*—(1) *Content of penicillin, streptomycin, and dihydrostreptomycin.* Proceed as directed in § 141a.35(a).

(2) *Bacitracin content.* Proceed as directed in § 141e.402 (a) of this chapter, except that:

(i) Sufficient penicillinase is added to the sample under test to completely inactivate the penicillin present.

(ii) Use as the test organism the streptomycin dihydrostreptomycin-resistant strain of either Micrococcus flavus (ATCC 10240A) or Sarcina subflava (ATCC 7468/d), grown and maintained in media containing 500 micrograms of streptomycin or dihydrostreptomycin per milliliter of media, or calculate from the quantity of streptomycin or dihydrostreptomycin found, using the method prescribed by subparagraph (1) of this paragraph, the quantity that would be present when the sample is diluted to contain one unit of bacitracin (labeled potency) per milliliter. Prepare the bacitracin standard curve by adding the calculated quantity of streptomycin or dihydrostreptomycin to each concentration of bacitracin used for the curve. Use this standard curve to calculate the bacitracin content of the sample.

(3) *Bacitracin methylene disalicylate content.* Proceed as directed in subparagraph (2) of this paragraph, except prepare the sample as follows: Place a representative portion of the sample (usually approximately 1 gram, accurately weighed) or the entire contents of a single-dose container in blending jar, add 99 milliliters of a 2.0-percent aqueous solution of sodium bicarbonate and 1 milliliter of a 10-percent aqueous solution of polysorbate 80 and blend for 3 minutes in a high-speed blender. Allow the foam to subside, remove an aliquot of the solution, and dilute to 1 unit per milliliter with 1.0-percent phosphate buffer, pH 6.0.

(b) *Moisture.* Proceed as directed in § 141a.8 (b).

§ 141a.50 Penicillin-streptomycin dental cones; penicillin-dihydrostreptomycin dental cones.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.9(a). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Steptomycin content.* Proceed as directed in § 141a.36 (a) (2). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in § 141a.36 (a) (3). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.51 Diethylaminoethyl ester penicillin G hydriodide.

(a) *Potency.* Proceed as directed in § 141a.1, except prepare the sample as follows: Dissolve in 0.1 *M* potassium phosphate buffer (pH 7.8–8.0) to make a stock solution of 100 units per milliliter (estimated). Allow to stand at room temperature for not less than 1.5 hours and not more than 2 hours and then dilute an aliquot with 1-percent phosphate buffer (pH 6.0) to 1.0 unit (estimated), or proceed by the iodometric method described in § 141a.5(d)(1), except prepare the sample as follows: Dissolve a weighed sample (approximately 50 milligrams) in 2.0 milliliters of redistilled methanol. Further dilute this solution with 1-percent phosphate buffer (pH 6.0) to give a concentration of 2,000 units per milliliter.

(b) *Sterility.* Proceed as directed in § 141a.2, except in the test for bacteria add for each 100 milliliters of media used 0.5 milliliter of polysorbate 80 and a sufficient quantity of 2 *N* NaOH to produce a solution having a pH of approximately 7.9 after sterilization.

(c) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent.

(d) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent, and inject 0.5 milliliter of a solution containing 2,000 units per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.5 (a).

(f) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution prepared by adding 300 milligrams per milliliter.

(g) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(h) *Penicillin G content.* Accurately weigh approximately 50 milligrams of the sample and dissolve in 25-milliliter potassium phosphate buffer, pH 7.9 (one part of 0.1 *M* KH_2PO_4, and 11.66 parts of 0.1 *M* K_2HPO_4). Allow to stand at room temperature for not less than 1.5 hours and not more than 2 hours. Transfer a 5.0-milliliter aliquot to a 25-milliliter glass-stoppered test tube. Place the tube in an ice bath and add 10.0 milliliters of chloroform (previously washed with water). After cooling, adjust the pH of the aqueous phase to 2.0 by adding 0.5 milliliter of 1–4 H_3PO_4. Shake the tube thoroughly for 2 minutes, centrifuge, and withdraw the lower chloroform layer with the aid of a 10-milliliter hypodermic syringe and a 3-inch needle. Superficially dry the chloroform by filtering through a pledget of cotton, using a U-shaped funnel to reduce evaporation during filtration. Determine the absorbance of the filtered chloroform solution in a 1-centimeter cell at 265 mμ and 280 mμ, using a suitable spectrophotometer. Treat the working standard of sodium penicillin G in the same manner, using an accurately weighed sample of approximately 30 milligrams.

$$\text{Percent penicillin G} = \frac{(A_x \text{ at } 265 \text{ m}\mu - A_x \text{ at } 280 \text{ m}\mu)(\text{wt. } s)(100)}{(A_s \text{ at } 265 \text{ m}\mu - A_s \text{ at } 280 \text{ m}\mu)(\text{wt. } x)(0.635)},$$

where:

A = absorbance.
x = diethylaminoethyl ester penicillin G hydriodide.
s = sodium penicillin G working standard.

§ 141a.52 Diethylaminoethyl ester penicillin G hydriodide for aqueous injection.

(a) *Potency.* Using a representative aliquot of the product reconstituted as directed in the labeling, proceed as directed in § 141a.51(a). Its potency is satisfactory if it contains not less than 90 percent of the number of units that it is represented to contain.

(b) *Sterility.* Use the entire contents of single-dose containers or the equivalent of approximately 300 milligrams (activity) from each multiple-dose container, and proceed as directed in § 141a.51.

(c) *Moisture.* Proceed as directed in § 141a.5 (a).

(d) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent.

(e) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent, and inject 0.5 milliliter of a solution containing 2,000 units per milliliter.

(f) *pH.* Proceed as directed in § 141a.5(b), using the suspension resulting when the product is reconstituted as directed in the labeling.

§ 141a.53 Penicillin-streptomycin implantation pellets; penicillin-dihydrostreptomycin implantation pellets.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.9(a). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141a.36 (a) (2). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in § 141a.36 (a) (3). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.54 Benzathine penicillin G for aqueous injection.

(a) *Potency.* Proceed as directed in § 141a.47(a), using as the sample for assay a representative aliquot of the suspension equivalent to one dose; or

if it is a dry mixture of the drug, a representative aliquot of the drug equivalent to one dose after it has been reconstituted as directed in the labeling. Its potency is satisfactory if it contains not less than 90 percent of the number of units that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.47 (b).

(c) *Moisture (dry mixture of the drug).* Proceed as directed in § 141a.26 (e).

(d) *Pyrogens.* Proceed as directed in § 141a.47 (d).

(e) *Toxicity.* Proceed as directed in § 141a.47 (c).

(f) *pH*—(1) *Dry mixture of the drug.* Proceed as directed in § 141a.5(b), using the suspension resulting when the product is reconstituted as directed in the labeling.

(2) *Aqueous suspension of the drug.* Proceed as directed in § 141a.5(b), using the undiluted aqueous suspension.

§ 141a.55 Benzathine penicillin G and buffered crystalline penicillin for aqueous injection.

(a) *Total potency (except in single-dose containers).* Proceed as directed in § 141a.1, except if the bioassay method is used prepare the sample by diluting 1.0 milliliter of the drug suspension with sufficient dimethyl formamide, formamide, or methyl alcohol to dissolve the benzathine penicillin. Make to 100 milliliters with buffer. Shake well and dilute to 1.0 unit per milliliter. If the iodometric method is used, proceed as directed in § 141a.47, except in preparing the blank solution dilute 1.0 milliliter of the drug suspension to 250 milliliters with 1-percent phosphate buffer at pH 6.0. In preparing the solution for inactivation dissolve 1.0 milliliter of the drug suspension in approximately 20 milliliters of 0.5 *N* NaOH. Allow to stand for 15 minutes. Dilute to 250 milliliters with distilled water. Pipette a 2.0-milliliter aliquot into a 125-milliliter glass-stoppered Erlenmeyer flask and add 2.0 milliliters 1.2 *N* HCl and 10 milliliters 0.01 *N* iodine.

(b) *Buffered crystalline penicillin content.* Place 1.0 milliliter of the drug suspension in a 10-milliliter volumetric flask and add 20 percent sodium sulfate to make 10 milliliters. Shake well and centrifuge to obtain a clear, or reasonably clear, solution. Dilute a 5.0-milliliter aliquot to 50 milliliters with buffer and proceed as directed in § 141a.1 to determine the number of units per milliliter of this solution, and from this value calculate the number of units per milliliter of the drug. The content of buffered crystalline penicillin is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(c) *Benzathine penicillin G content.* The benzathine penicillin G content of the batch is the difference between the total potency as described in paragraph (a) or (d) of this section and the content of buffered crystalline penicillin determined by the method prescribed in paragraph (b) of this section. The content of benzathine penicillin G is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(d) *Total potency of a single-dose container.* Add sufficient distilled water to the material remaining in the 10-milliliter volumetric flask referred to in paragraph (b) of this section to bring the volume back to 10 milliliters and determine the number of units per milliliter of this suspension. If the iodometric method is used, 2.0-milliliter aliquots are placed in 50-milliliter volumetric flasks (one blank and one to be inactivated). Obtain the total potency by adding the number of units found in the 10-milliliter volumetric flask to one-half the content of buffered crystalline penicillin found in paragraph (b) of this section.

(e) *Sterility.* Proceed as directed in § 141a.47 (b).

(f) *Moisture.* Proceed as directed in § 141a.26 (e).

(g) *Pyrogens.* Proceed as directed in § 141a.47 (d).

(h) *Toxicity.* Proceed as directed in § 141a.47 (c).

(i) *pH.* Proceed as directed in § 141a.5(b), using the suspension resulting when the product is reconstituted as directed in the labeling.

§ 141a.56 Chloroprocaine penicillin O.

(a) *Potency, sterility, pyrogens, toxicity, moisture, pH, and crystallinity.* Proceed as directed in § 141a.26, except if the iodometric assay for potency is used, calculate as directed in § 141a.5(d) (2).

(b) *Chloroprocaine penicillin O content.* Proceed as directed in § 141a.5 (h) (1), except use an accurately weighed sample of approximately 168 milligrams and calculate the percent of chloroprocaine penicillin O as follows:

$$\frac{a\ (\text{sample})}{a\ (\text{standard})} \times 168 = \text{percent chloroprocaine penicillin O.}$$

(c) *Chloroprocaine penicillin G content.* Proceed as directed in § 141a.5 (g), except prepare the sample as follows: Accurately weigh approximately 500 milligrams of the sample in a 25-milliliter glass-stoppered test tube. Add 6 milliliters of distilled water and 6.0 milliliters of amyl acetate. Place the tube in an ice bath for 5 minutes and then add 4 milliliters of 1–4 H_3PO_4, shake vigorously for 2 minutes, centrifuge for 1 minute to separate the layers, and withdraw 5.0 milliliters of the amyl acetate layer. Place the amyl acetate in a 250-milliliter Erlenmeyer flask and evaporate to dryness by directing a stream of air into the flask. Dissolve the residue in 2.0 milliliters of 2.5 percent KOH.

Calculate the percent of penicillin G in the sample from the equation:

$$\frac{(5.10)\,(x)\,(50)\,(100)}{(\text{Wt. sample milligrams})\,(0.833)} = \text{percent penicillin G}$$

§ 141a.57 Chloroprocaine penicillin O for aqueous injection.

For the determination of potency, sterility, moisture, pyrogens, toxicity, and pH, proceed as directed in § 141a.29, except if the iodometric assay for potency is used, calculate as directed in § 141a.5(d) (2).

§ 141a.58 Penicillin-streptomycin vaginal suppositories; penicillin-dihydrostreptomycin vaginal suppositories.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.18(a). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Using 5 suppositories, proceed as directed in § 141a.35 (a) (2), except that 150 milliliters of peroxide-free ether is used in the extraction. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (2) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.18 (b).

§ 141a.59 Penicillin—streptomycin-bacitracin dental paste; penicillin-dihydrostreptomycin—bacitracin dental paste.

(a) *Potency.* Proceed as directed in § 141a.49(a).

(b) *Moisture.* Proceed as directed in § 141a.8 (b).

(c) *Sterility.* Proceed as directed in §141a.7 (b).

§ 141a.60 Penicillin and dihydrostreptomycin-streptomycin sulfates veterinary; procaine penicillin in dihydrostreptomycin-streptomycin sulfates solution veterinary.

(a) *Potency.* Use as the sample for assay a representative aliquot of the suspension equivalent to one dose; or if it is a dry mixture of the drug, a representative aliquot of the drug equivalent to one dose after it has been reconstituted as directed in the labeling.

(1) *Penicillin content.* If it contains:

(i) *Crystalline penicillin and dihydrostreptomycin-streptomycin sulfates.* Proceed as directed in § 141a.39(a) (2) if it is the dry powder or in § 141a.46(a) (1) if it is the solution; or

(ii) *Procaine penicillin and dihydrostreptomycin-streptomycin sulfates.* Proceed as directed in § 141a.39(a) (2) if it is the dry powder or in § 141a.46(a) (1) if it is the solution; or

(iii) *Benzathine penicillin G and dihydrostreptomycin - streptomycin sulfates.* Proceed as directed in § 141a.47 (a), except that in the iodometric assay 1 drop of 1.2 *N* HCl is added to the blank immediately before the addition of the 0.01 *N* I_2; or

(iv) *Crystalline penicillin-procaine penicillin and dihydrostreptomycin-streptomycin sulfates.* Proceed as directed in § 141a.32 (a), (b), and (c), except that in the iodometric assay 1 drop of 1.2 *N* HCl is added to each blank im-

mediately before the addition of the 0.01 *N* I_2; or

(v) *Crystalline penicillin-benzathine penicillin G and dihydrostreptomycin-streptomycin sulfates.* Proceed as directed in § 141a.55 (a), (b), (c), and (d), except that in the iodometric assay 1 drop of 1.2 *N* HCl is added to each blank immediately before the addition of the 0.01 *N* I_2; or

(vi) *Crystalline penicillin-procaine penicillin-benzathine penicillin G and dihydrostreptomycin-streptomycin sulfates.* Proceed as directed in § 141a.61 (a) (1), (2), (3), and (4), except that in the iodometric assay 1 drop of 1.2 *N* HCl is added to each blank immediately before the addition of the 0.01 *N* I_2; or

(vii) *Crystalline penicillin O-chloroprocaine penicillin O and dihydrostreptomycin-streptomycin sulfates.* Proceed as directed in § 141a.32 (a), (b), (c), and (d), with the following exceptions:

(*a*) In the iodometric assay, 1 drop of 1.2 *N* HCl is added to the blank immediately before the addition of the 0.01 *N* I_2.

(*b*) The penicillin O working standard is used as the standard of comparison in the iodometric assay.

(*c*) In the colorimetric determination of chloroprocaine penicillin O, the standard curve is prepared by using a standard solution containing 31.04 milligrams of chloroprocaine hydrochloride in 1 liter of distilled water; or

(viii) *Procaine penicillin-benzathine penicillin G and dihydrostreptomycin-streptomycin sulfates.* Proceed as directed in § 141a.67 (a) (1) and (2).

The total potency and the number of units of each salt of penicillin are satisfactory if the immediate containers contain not less than 85 percent of the number of units that they are represented to contain.

(2) *Combined potency of dihydrostreptomycin and streptomycin; content of streptomycin.* Proceed as directed in § 141b.118 (a) and (b) of this chapter. Its combined potency of streptomycin and dihydrostreptomycin is satisfactory if it is not less than 90 percent of the number of milligrams that it is represented to contain. Its content of streptomycin is satisfactory if it contains not less than 45 percent and not more than 55 percent of the combined potency of streptomycin and dihydrostreptomycin.

(b) *Sterility.* Proceed as directed in § 141a.39 (b), except if it contains benzathine penicillin G proceed as directed in § 141a.47 (b).

(c) *Toxicity.* Proceed as directed in § 141a.39 (c), except if it contains benzathine penicillin G, proceed as directed in § 141a.47 (c), using a test suspension containing a total penicillin activity of 4,000 units per milliliter.

(d) *Pyrogens.* Proceed as directed in § 141a.39 (d), except if it contains benzathine penicillin G proceed as directed in § 141a.47 (c), using a test suspension containing a total penicillin activity of 4,000 units per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.5 (a), except if it contains procaine penicillin, chloroprocaine penicillin O, or benzathine penicillin G proceed as directed in § 141a.26(e).

(f) *pH.* Proceed as directed in § 141a.29 (f).

§ 141a.61 Benzathine-procaine-buffered crystalline penicillins for aqueous injection.

(a) *Potency*—(1) *Total potency.* Proceed as directed in § 141a.1, except if the bioassay method is used prepare the sample by diluting one dose of the drug suspension with sufficient dimethyl formamide or formamide or methyl alcohol to dissolve the benzathine penicillin G. Make to 100 milliliters with 1-percent phosphate buffer, pH 6.0. Shake well, and dilute to 1.0 unit per milliliter with buffer. If the iodometric method of assay is used, add the indicated amount of distilled water to the contents of a vial of the sample, shake well, and proceed as follows (except for single-dose containers):

(i) Using a standardized hypodermic syringe, withdraw one dose and dilute with 1-percent phosphate buffer, pH 6.0, to give a concentration of approximately 2,000 units per milliliter. Use 2.0 milliliters of this suspension as the blank in the iodometric assay procedure described in § 141a.5 (d) (1).

(ii) Using a standardized hypodermic syringe, withdraw another dose, place in a flask, and add 20 milliliters of 0.5 *N* NaOH for each 300,000 units of benzathine penicillin, mix well, being sure that all penicillin is in solution, and allow to stand for 15 minutes. Add 1 milliliter of 1.2 *N* HCl for each 2 milliliters of 0.5 *N* NaOH, mix, and dilute with distilled water to the same volume as was used in subdivision (i) of this subparagraph. Place 2.0 milliliters in a 125-milliliter glass-stoppered Erlenmeyer flask, add 10 milliliters of 0.01 *N* iodine, allow to stand for 15 minutes, and titrate with 0.01 *N* sodium thiosulfate as directed in the iodometric assay procedure in § 141a.5 (d) (1). The total potency of the batch is satisfactory if it contains not less than 85 percent of that which it is represented to contain.

(2) *Procaine penicillin content (except for single-dose containers).* Make suitable dilutions of the solution prepared in subparagraph (1) (ii) of this paragraph to obtain approximately 60 units of procaine penicillin per milliliter. Determine the procaine penicillin content by the colorimetric procedure described in § 141a.32 (b) (3). The content of procaine penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(3) *Buffered crystalline penicillin content*—(i) *Preparation of the solution for assay.* (*a*) Add the indicated amount of distilled water to the contents of a vial of the sample, and shake well. Withdraw one dose of the suspension with a hypodermic syringe and place in a 10-milliliter volumetric flask. Add 20-percent sodium sulfate solution almost to the mark, centrifuge sufficiently to see the meniscus, make to volume with 20-percent sodium sulfate solution, shake well, and centrifuge to obtain a clear or reasonably clear solution; or

(*b*) If the original product contains more than 600,000 units, place it in a 50-milliliter volumetric flask, add 20-percent sodium sulfate to the mark, shake well, place a 10-milliliter portion in a centrifuge tube, and centrifuge to obtain a reasonably clear solution.

(*c*) Dilute a 5.0-milliliter aliquot of the clear solution obtained in (*a*) or (*b*) of this subdivision with 1-percent phosphate buffer, pH 6.0, to give a solution for assay of approximately 2,000 units per milliliter.

(ii) *Iodometric assay for total penicillin in the solution for assay.* Determine the total quantity of penicillin in the solution for assay by the iodometric assay procedure described in § 141a.5 (d) (1).

(iii) *Colorimetric determination of procaine penicillin in the solution for assay.* Proceed as directed in § 141a.32 (b) (3). The content of procaine penicillin in the batch is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(iv) The buffered crystalline penicillin in one dose of the product is calculated as follows:

$$A = (B - C)F,$$

where

A = the buffered crystalline penicillin content of the product.

B = the number of units of penicillin per milliliter as determined in subparagraph (3) (ii) of this paragraph.

C = the number of units of procaine penicillin per milliliter as determined in subparagraph (3) (iii) of this paragraph.

F = the appropriate dilution factor depending on the dilutions made in the preparation of the solution for assay.

The content of buffered crystalline penicillin is satisfactory if the batch contains 85 percent of the number of units per milliliter that it is represented to contain.

(4) *Benzathine penicillin content.* The sum of the procaine penicillin content determined under subparagraph (2) or (6) of this paragraph and the buffered crystalline penicillin content determined under subparagraph (3) of this paragraph, subtracted from the total potency determined in subparagraph (1) or (5) of this paragraph, represents the benzathine penicillin G content. The benzathine penicillin G content is satisfactory if it is not less than 85 percent of the number of units that it is represented to contain.

(5) *Total potency of a single-dose container.* Wash out the material remaining in the volumetric flask referred to in subparagraph (3) (i) (*a*) of this paragraph, or combine the contents remaining in the 50-milliliter volumetric flask and in the centrifuge tube referred to in subparagraph (3) (i) (*b*) of this paragraph. Dissolve the material by adding 10 milliliters of 1 *N* NaOH for each 300,000 units of benzathine penicillin and allow to stand 15 minutes. Add 1 milliliter of 1.2 *N* HCl for each milliliter of 1 *N* NaOH and then dilute with distilled water to give a concentration of approximately 2,000 units per milliliter. Place 2.0 milliliters in a 125-milliliter glass-stoppered Erlenmeyer flask, add 10 milliliters of 0.01 *N* iodine, allow to stand for 15 minutes, and then titrate with 0.01 *N* sodium thiosulfate

as directed in § 141a.5 (d) (1). For the blank determination prepare a separate sample as directed in subparagraph (3) (i) (*a*) or (*b*) of this paragraph and in the first sentence of this subparagraph, then dilute with 1 percent phosphate buffer, pH 6.0, to give a concentration of approximately 2,000 units per milliliter. The total potency of the one-dose container is equal to the sum of the number of units found in this assay (units per milliliter×volume) and the number of units found (units per milliliter ×volume) in the solution for assay in subparagraph (3) (ii) of this paragraph.

(6) *Procaine penicillin content of a single-dose container.* Make suitable dilutions of the NaOH-inactivated solution prepared in subparagraph (5) of this paragraph to obtain approximately 60 units of procaine penicillin per milliliter. Determine the procaine penicillin content (units per milliliter× volume) of this solution by the colorimetric procedure described under § 141a.32 (b) (3). To this value add the procaine penicillin content (units per milliliter×volume) of the solution for assay, as found in subparagraph (3) (iii) of this paragraph, to obtain the procaine penicillin content of the one-dose container. The content of procaine penicillin in the batch is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.47 (b).

(c) *Pyrogens.* Proceed as directed in § 141a.47 (d).

(d) *Toxicity.* Proceed as directed in § 141a.47 (c).

(e) *Moisture.* Proceed as directed in § 141a.26 (e).

(f) *pH.* Proceed as directed in § 141a.5(b), using the suspension resulting when the product is reconstituted as directed in the labeling.

§ 141a.62 Benzathine penicillin G and procaine penicillin for aqueous injection.

(a) *Total potency, benzathine penicillin G content, procaine penicillin content.* Proceed as directed in § 141a.61 (a) (1), (2), and (4).

(b) *Sterility, toxicity, pyrogens.* Proceed as directed in § 141a.47 (b), (c), and (d).

(c) *pH.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension or the suspension prepared as directed in the labeling for the drug.

(d) *Moisture (dry mixture of the drug).* Proceed as directed in § 141.26 (e).

§ 141a.63 Penicillin-bacitracin-neomycin ointment; penicillin-bacitracin-neomycin in oil.

(a) *Potency*—(1) *Penicillin content; bacitracin content.* Proceed as directed in § 141a.37(a).

(2) *Neomycin content.* Proceed as directed in § 141e.411 (a) (2) of this chapter, except that sufficient penicillinase is added to the sample under test to completely inactivate the penicillin present. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b).

§ 141a.64 Penicillin-streptomycin tablets; penicillin-dihydrostreptomycin tablets.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.9(a). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141a.36 (a) (2). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in § 141a.36 (a) (3). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

(c) *Disintegration time.* Proceed as directed in § 141a.9(c).

§ 141a.65 Penicillin-streptomycin-neomycin in oil; penicillin-dihydrostreptomycin-neomycin in oil; penicillin-streptomycin-neomycin ointment; penicillin-dihydrostreptomycin-neomycin ointment.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.35(a) (1), (2), and (3). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141b.101 of this chapter, except § 141b.101 (j) and (k) of this chapter, and in lieu of the directions in § 141b.101 (e) of this chapter, prepare the sample as directed in § 141a.35 (a) (4) (i). If the sample contains three times as much (or more) neomycin as streptomycin, prepare the streptomycin standard curve by adding to each concentration of streptomycin the quantity of neomycin (as calculated from the quantity of neomycin found, using the method prescribed in subparagraph (4) of this paragraph) that would be present when the sample is diluted to contain 1.0 μg. of streptomycin (estimated) per milliliter. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (2) of this paragraph, using the dihydrostreptomycin working standard as the standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(4) *Neomycin content.* (i) Proceed as directed in § 141e.410(b) (1) of this chapter, except prepare the sample as follows: Place 1.0 milliliter of the sample in a separatory funnel containing approximately 50 milliliters of peroxide-free ether and extract with four successive 20-milliliter portions of distilled water. Make the combined aqueous extractions to 100 milliliters with distilled water. Transfer a 10-milliliter aliquot of the aqueous extract to a 25-milliliter volumetric flask and add 1.0 milliliter of 5 percent $Ba(OH)_2 8H_2O$. Using a test-tube clamp, suspend the open flask in a steam bath so that the mouth of the flask is slightly above the level of the steam bath. Heat with steam for 3 hours; remove, cool, add one drop of 1.0 percent phenolphthalein and neutralize dropwise with 1.0 *N* H_2SO_4. Make to volume with distilled water and pour a reasonable aliquot into an appropriate centrifuging tube. Centrifuge for 5 minutes at approximately 4,000 r.p.m. and decant. Pipette an appropriate volume for assay and accurately add sufficient 1.0 *M* potassium phosphate buffer, pH 8.0, to provide, after addition of distilled water, a solution having a molarity of 0.1 percent with respect to the potassium phosphate buffer and containing 10 micrograms of neomycin per milliliter if the test organism is Staphylococcus aureus, and 1.0 microgram of neomycin per milliliter if the test organism is Staphylococcus epidermidis.

(ii) The neomycin content may also be determined as follows: Place 1.0 milliliter of the sample in a separatory funnel containing 50 milliliters of peroxide-free ether and extract with four successive 20-milliliter portions of 0.1 *M* potassium phosphate buffer at pH 7.8 to 8.0. Make the combined aqueous extractions to 100 milliliters with the 0.1 *M* potassium phosphate buffer. Pipette an appropriate volume for assay and accurately add sufficient 0.1 *M* potassium phosphate buffer to provide a solution containing 10 micrograms of neomycin per milliliter if the test organism is Staphylococcus aureus and 1.0 microgram of neomycin per milliliter if the test organism is Staphylococcus epidermidis. Proceed as directed in § 141b.410(b) (1) of this chapter, except add sufficient penicillinase to completely inactivate the penicillin present. If Staphylococcus aureus is used as the test organism, use the Food and Drug Administration dihydrostreptomycin-resistant strain of Staphylococcus aureus (A.T.C.C. 6538–PR) which is grown and maintained on media containing 1,000 micrograms of dihydrostreptomycin per milliliter of agar.

(b) *Moisture.* Using 1 milliliter as the test sample, proceed as directed in § 141a.7 (c).

§ 141a.66 Capsules procaine penicillin in oil.

(a) *Potency.* Proceed as directed in § 141a.1, except paragraph (i) of that section, and in lieu of the directions in § 141a.1(d) prepare the sample as follows: Place 12 capsules in a blending jar containing 40 milliliters of absolute alcohol and 200 milliliters of 1.0 percent phosphate buffer, pH 6.0. After blending for 1 minute with a high-speed blender, add 260 milliliters of 1.0 percent phosphate buffer, pH 6.0. Blend again for 1 minute and make the proper estimated dilutions in 1-percent phosphate buffer at pH 6.0. Its potency is satisfactory if it contains not less than 85 percent of the number of units per capsule that it is represented to contain.

(b) *Moisture.* Using an accurately weighed sample of approximately 1 gram of the capsule contents, proceed as directed in § 141a.7 (c).

§ 141a.67 Procaine penicillin and benzathine penicillin G in streptomycin sulfate solution; procaine penicillin and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (procaine penicillin and benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).

(a) *Potency*—(1) *Total potency and procaine penicillin content.* Proceed as directed in § 141a.61(a) (1) and (2), except that in the iodometric assay one drop of 1.2 *N* HCl is added to the blank immediately, before the addition of the 0.01 *N* iodine.

(2) *Benzathine penicillin G content.* The difference between the total penicillin potency and the procaine penicillin content determined under subparagraph (1) of this paragraph represents the benzathine penicillin G content. The benzathine penicillin G content is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(3) *Streptomycin content.* Proceed as directed in § 141b.101 (j) and (k) of this chapter.

(4) *Dihydrostreptomycin content.* Proceed as directed in § 141b.108 (a) of this chapter.

(b) *Sterility.* Proceed as directed in § 141a.47 (b), except that no control tube is used in the test for bacteria.

(c) *Toxicity.* Proceed as directed in § 141a.39 (c).

(d) *Pyrogens.* Proceed as directed in § 141a.39 (d).

(e) *pH.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension.

§ 141a.68 Benzathine penicillin G and streptomycin; benzathine penicillin G and dihydrostreptomycin veterinary.

(a) *Potency*—(1) *Content of benzathine penicillin G.* Proceed as directed in § 141a.47(a). Its content of benzathine penicillin G is satisfactory if it contains not less than 90 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141b.101 (j) of this chapter. Its content of streptomycin is satisfactory if it contains not less than 90 percent of the number of grams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in § 141b.108 (a) of this chapter. Its content of dihydrostreptomycin is satisfactory if it contains not less than 90 percent of the number of grams that it is represented to contain.

(b) *Sterility.* Use the entire contents of single-dose containers or the equivalent of approximately 0.5 gram (combined activity) for each multiple-dose container, and proceed as directed in § 141a.47 (b), except that no control tube is used in the test for bacteria.

(c) *Moisture.* Proceed as directed in § 141a.26 (e).

(d) *Toxicity, pyrogens, pH.* Proceed as directed in § 141a.39 (c), (d), and (f).

§ 141a.69 Crystalline penicillin G oral suspension, crystalline penicillin G sodium oral suspension, potassium penicillin G oral suspension.

(a) *Potency.* Proceed as directed in § 141a.1, except § 141a.1(i), and in lieu of the directions in § 141a.1(d), prepare the sample as follows: By means of a hypodermic syringe, introduce 5 milliliters of the well-shaken test sample into a high-speed blender containing 244 milliliters of 1-percent phosphate buffer at pH 6.0 and 1.0 milliliter of polysorbate 80. Blend the mixture for 3 to 5 minutes. Make the proper estimated dilutions in 1-percent phosphate buffer at pH 6.0. Its potency is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.70 Tablets benzathine penicillin G and crystalline penicillin.

(a) *Potency*—(1) *Total potency.* Proceed as directed in § 141a.9(a)(2). Its total potency is satisfactory if it contains not less than 85 percent of the number of units per tablet that it is represented to contain.

(2) *Crystalline penicillin content.* Place 5 tablets in a blending jar and add thereto sufficient distilled water to give a concentration of 5,000 units of crystalline penicillin per milliliter. Blend for 2 minutes with a high-speed blender, filter, remove a 10-milliliter aliquot of the filtrate and dilute to 25 milliliters with 1.0 percent phosphate buffer at pH 6.0. Remove a 2-milliliter aliquot of this solution and assay by the iodometric assay procedure described in § 141a.5 (d) (1). Its content of crystalline penicillin is satisfactory if it contains not less than 85 percent of the number of units per tablet that it is represented to contain.

(3) *Benzathine penicillin G content.* The benzathine penicillin G content of the batch is the difference between the total potency as determined by the method described in subparagraph (1) of this paragraph and the content of crystalline penicillin as determined by the method prescribed in subparagraph (2) of this paragraph. Its content of benzathine penicillin G is satisfactory if it contains not less than 85 percent of the number of units per tablet that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.26 (e).

(c) *Disintegration time.* Proceed as directed in § 141a.9(c).

§ 141a.71 Penicillin-streptomycin powder; penicillin-dihydrostreptomycin powder.

(a) *Potency*—(1) *Penicillin content.* Use an accurately weighed sample of approximately 1 gram and proceed as directed in § 141a.1, except paragraph (i) of that section. The penicillin content of the powder is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Use an accurately weighed sample of approximately 1 gram and proceed as directed in § 141a.36 (a) (2). The streptomycin content of the powder is satisfactory if it contains not less than 85 percent of the number of milligrams of activity that it is represented to contain.

(3) *Dihydrostreptomycin content.* Use an accurately weighed sample of approximately 1 gram and proceed as directed in § 141a.36 (a) (3). The dihydrostreptomycin content of the powder is satisfactory if it contains not less than 85 percent of the number of milligrams of activity that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.72 Dibenzylamine penicillin G (dibenzylamine penicillin G salt).

(a) *Potency.* Proceeds as directed in § 141a.26 (a).

(b) *Sterility.* Proceed as directed in § 141a.2.

(c) *Pyrogens.* Proceed as directed in § 141a.3, except use physiological salt solution as the diluent.

(d) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent, and inject 0.25 milliliter of a solution containing 4,000 units per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.26 (e).

(f) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution prepared by adding 300 milligrams per milliliter.

(g) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(h) *Penicillin G content.* Proceed as directed in § 141a.26 (h), using the following formula for calculating the percent of dibenzylamine penicillin G:

$$\text{Percent of dibenzylamine penicillin G} = \frac{\text{N-ethyl piperidine penicillin precipitate} \times 245.5}{\text{Weight of sample in milligrams}}$$

§ 141a.73 Dibenzylamine penicillin and potassium penicillin powder, buffered.

(a) *Total potency.* Proceed as directed in § 141a.1, using 5 milliliters of the preparation, reconstituted as directed in the labeling.

(b) *Potassium penicillin content.* Centrifuge approximately 10 milliliters of the reconstituted preparation to obtain a clear solution and proceed as directed in § 141a.1, using 5 milliliters of the clear solution. The potency of the clear solution is regarded as the potassium penicillin content. The content of potassium penicillin is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(c) *Dibenzylamine penicillin content.* The difference between the total potency

as determined by paragraph (a) of this section and the potassium penicillin as determined by paragraph (b) of this section represents the amount of dibenzylamine penicillin present. The content of dibenzylamine penicillin is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(d) *Moisture.* Proceed as directed in § 141a.26 (e).

(e) *pH.* Proceed as directed in § 141a.5 (b), using the suspension resulting when the product is reconstituted as directed in the labeling.

§ 141a.74 Dibenzylamine penicillin and streptomycin in oil; dibenzylamine penicillin and dihydrostreptomycin in oil.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.27 (a), except the last sentence thereof. Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(2) *Streptomycin content.* Using 1.0 milliliter as the test sample, proceed as directed in § 141a.35 (a) (2). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(3) *Dihydrostreptomycin content.* Using 1.0 milliliter as the test sample, proceed as directed in § 141a.35 (a) (3). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(b) *Moisture.* Using 1.0 milliliter as the test sample, proceed as directed in § 141a.7 (c).

§ 141a.75 Hydrabamine penicillin G.

(a) *Potency.* Proceed as directed in § 141a.1, except if the bioassay method is used prepare the sample as follows: Dissolve an accurately weighed sample in methanol and dilute with methanol to 1,000 units per milliliter (estimated). By means of a volumetric pipette, add dropwise a 1.0-milliliter aliquot to a 1,000-milliliter volumetric flask containing approximately 800 milliliters of 1-percent phosphate buffer, pH 6.0, constantly swirling the flask during the addition. Make to a volume of 1,000 milliliters with 1-percent phosphate buffer, pH 6.0. If the iodometric method is used, accurately weigh 30–50 milligrams of the sample to be tested in a 50-milliliter Erlenmeyer flask and dissolve in sufficient chloroform U.S.P. to give a concentration of 2.0 milligrams per milliliter. Pipette 2.0 milliliters of this solution into a 125-milliliter glass-stoppered Erlenmeyer flask, add 10 milliliters of 0.01 *N* I_2 and titrate immediately with 0.01 *N* $Na_2S_2O_3$ for the blank determination. Toward the end of the titration add 1 drop of starch solution or about 5.0 milliliters of CCl_4. Continue the titration by the addition of 0.01–0.02-milliliter portions of 0.01 *N* $Na_2S_2O_3$, shaking vigorously after each addition. The end point is reached when the blue color of the starch-iodine complex is discharged or when the CCl_4 layer becomes colorless. Prepare the solution of inactivated penicillin as follows: To 10 milliliters of the original chloroform solution add 10 milliliters of 1 *N* NaOH and shake well immediately and 5 minutes later. Fifteen minutes after the initial shaking, pipette 2.0 milliliters of the upper NaOH layer into a 125-milliliter glass-stoppered Erlenmeyer flask, add 2.0 milliliters of 1.2 *N* HCl and 10 milliliters of 0.01 *N* I_2. Stopper the flask. After 15 minutes, titrate the excess iodine with 0.01 *N* $Na_2S_2O_3$.

$$\text{Units of hydrabamine penicillin G per milligram} = \frac{\text{Difference in titers} \times \text{potency of F. D. A. working standard in units per milligram}}{4 \times F}$$

where F = the number of milliliters of 0.01 *N* I_2 absorbed for each 1.0 milligram of the Food and Drug Administration sodium penicillin G working standard.

(b) *Toxicity.* Proceed as directed in § 141a.4, except use 0.5 percent gum arabic solution as the diluent and inject 0.25 milliliter of a suspension containing 4,000 units per milliliter.

(c) *Moisture.* Proceed as directed in § 141a.26 (e).

(d) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution prepared by adding approximately 60 milligrams per milliliter.

(e) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(f) *Penicillin G content.* Accurately weigh a glass weighing bottle of approximately 10-milliliter capacity together with its top, a stirring rod, and a medium-porosity immersion filter stick. Transfer to the weighing bottle approximately 225 milligrams of the sample to be tested and reweigh. Add 1.5 milliliters of pyridine and stir until solution is complete. Add 0.25 milliliter of *N*-ethylpiperidine and stir until precipitation begins. When precipitation is complete, dilute with 2.5 milliliters of petroleum ether, stir well, and allow to stand for 15 minutes. Attach the filter stick to a vacuum line equipped with a suitable trap and withdraw the liquid from the precipitate. Add 2.5 milliliters of petroleum ether to the precipitate and withdraw the liquid from the precipitate. Repeat the procedure with two more 2.5-milliliter portions of petroleum ether. Leave the stirring rod and the filter stick in the bottle, dry for 30 minutes in a vacuum desiccator, stopper, and weigh.

$$\text{Percent of hydrabamine penicillin G} = \frac{\text{Milligrams of } N\text{-ethyl piperidine penicillin precipitate} \times 141.4}{\text{Weight of sample in milligrams}}$$

(g) *Absorptivity.* Accurately weigh approximately 100 milligrams of the sample, dissolve in absolute methyl alcohol, and make to 100 milliliters. Determine the absorptivity of the sample at the absorption peak at 276 mμ, using a suitable ultraviolet spectrophotometer and 1-centimeter quartz cells. Set the instrument to 100-percent transmission with absolute methyl alcohol. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 240 mμ to 300 mμ. If a nonrecording spectrophotometer is used, determine the absorbance of the solution at the 276 mμ absorption peak, using a slit width of 0.4 millimeter or less. (The exact position of the peak should be determined for the particular instrument used.) Calculate the absorptivity (1%, 1 cm.) of the sample at the absorption peak at 276 mμ.

§ 141a.76 Hydrabamine penicillin G oral suspension.

(a) *Potency.* Proceed as directed in § 141a.1, except if the bioassay method is used prepare the sample as follows: Place 1.0 milliliter of the sample to be tested in a 100-milliliter volumetric flask and dilute to volume with methanol. By means of a volumetric pipette add a 1.0-milliliter aliquot of this solution to a sufficient volume of 1-percent phosphate buffer pH 6.0 to give a solution having a concentration of 1 unit per milliliter (constantly swirling the flask during the addition). If the iodometric method is used, dilute 1.0 milliliter of the sample with sufficient 1-percent phosphate buffer pH 6.0 to produce a suspension containing 2,000 units per milliliter (estimated). Mix and pipette 2.0 milliliters into a 125-milliliter glass-stoppered Erlenmeyer flask. Add 10 milliliters of 0.01 *N* I_2 and titrate immediately with 0.01 *N* $Na_2S_2O_3$ for the blank determination. Dilute a second 1.0-milliliter portion of the sample with 1 *N* NaOH to produce a suspension containing 2,000 units per milliliter (estimated) and add approximately half that amount of chloroform U. S. P. Shake immediately and again after 5 minutes. Fifteen minutes after the initial shaking, pipette 2.0 milliliters of the upper NaOH layer into a 125-milliliter glass-stoppered Erlenmeyer flask and add 2.0 milliliters of 1.2 *N* HCl and 10 milliliters of 0.01 *N* I_2. After 15 minutes titrate the excess iodine with 0.01 *N* $Na_2S_2O_3$.

$$\text{Units of penicillin per milliliter of suspension} = \frac{\text{Difference in titers} \times \text{potency of F. D. A. working standard in units per milligram} \times \text{volume of 2,000 units per milliliter suspension}}{F \times 2}$$

where F = the number of milliliters of 0.01 *N* I_2 absorbed by 1.0 milligram of the Food and Drug Administration sodium penicillin G working standard.

(b) *pH.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension.

§ 141a.77 Capsules crystalline penicillin G (capsules crystalline penicillin G potassium, capsules crystalline penicillin G sodium).

(a) *Potency.* Use the contents of a representative number of capsules (usually 5 to 12) and proceed as directed in § 141a.1, except § 141a.1(i), and except if it contains a vegetable oil, prepare the sample as follows: Place the capsules in a blending jar containing 1.0 milliliter of polysorbate 80 and sufficient 1 percent phosphate buffer, pH 6.0, to give a volume of 250 milliliters. Using a high-speed blender, blend for 3 to 5 minutes, then add 250 milliliters of buffer and blend for an additional minute. Make further dilutions to 1 unit per milliliter (estimated) with 1 percent phosphate buffer, pH 6.0. The average potency of capsules crystalline penicillin G is satisfactory if it is not less than 85 percent of the number of units per capsule they are represented to contain.

(b) *Moisture.* Use the contents of 4 capsules and proceed as directed in § 141a.5 (a), except if it contains a vegetable oil proceed as directed in § 141a.7 (c).

§ 141a.78 Benzathine penicillin G in oil.

(a) *Potency.* Proceed as directed in § 141a.1, except paragraph (i) of that section, and in lieu of the directions in § 141a.1 (d) prepare the sample as follows: Place a representative quantity (usually 1.0 milliliter) of a multiple-dose container, or the entire contents of a single-dose container, in a blending jar containing sufficient dimethyl formamide (previously adjusted to a pH of 6.5±0.5 with concentrated H_2SO_4) or redistilled methanol to give a final volume of 100 milliliters. Using a high-speed blender, blend the mixture for 2 minutes and then make the proper estimated dilutions in a 1.0-percent phosphate buffer at pH 6.0. The potency is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.47 (b).

(c) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.79 Benzathine penicillin G and procaine penicillin G in oil.

(a) *Potency*—(1) *Total penicillin content.* Proceed as directed in § 141a.78(a). The total potency is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Procaine penicillin content.* Using an appropriate dilution of the solution prepared in subparagraph (1) of this paragraph, proceed as directed in § 141a.32 (b) (3). The procaine penicillin content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(3) *Benzathine penicillin G content.* The benzathine penicillin G content is the difference between the total penicillin content as determined in subparagraph (1) of this paragraph and the procaine penicillin content as determined in subparagraph (2) of this paragraph. The benzathine penicillin G content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.47 (b).

(c) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.80 Benzathine penicillin G-procaine penicillin G-streptomycin in oil; benzathine penicillin G-procaine penicillin G-dihydrostreptomycin in oil veterinary.

(a) *Potency*—(1) *Total penicillin content.* Proceed as directed in § 141a.79 (a) (1). The total penicillin content is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(2) *Procaine penicillin content.* Proceed as directed in § 141a.79 (a) (2). The procaine penicillin content is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(3) *Benzathine penicillin G content.* Proceed as directed in § 141a.79 (a) (3). The benzathine penicillin G content is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(4) *Streptomycin content.* Using a representative quantity (usually 1.0 milliliter) of a multiple-dose container, or the entire contents of a single-dose container, proceed as directed in § 141a.35 (a) (2). The streptomycin content is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(5) *Dihydrostreptomycin content.* Using a representative quantity (usually 1.0 milliliter) of a multiple-dose container, or the entire contents of a single-dose container, proceed as directed in § 141a.35 (a) (3). The dihydrostreptomycin content is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.47 (b).

(c) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.81 Penicillin V (phenoxymethyl penicillin).

(a) *Potency.* Using the penicillin V working standard as the standard of comparison, proceed as directed in § 141a.1, except prepare the sample as follows: Dissolve a weighed quantity of the sample (approximately 30 milligrams) in 2.0 milliliters of redistilled methanol. Further dilute this solution with sufficient 1 percent phosphate buffer, pH 6.0, to give a concentration of 2,000 units per milliliters (estimated) if the iodometric assay method is used, or 1.0 unit per milliliter (estimated) if the bioassay method is used.

(b) *Toxicity.* Proceed as directed in § 141a.4, except use physiological salt solution as the diluent, and inject 0.5 milliliter of a solution containing 2,000 units per milliliter.

(c) *Moisture.* Proceed as directed in § 141a.26 (e).

(d) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution prepared by adding 5 milligrams per milliliter.

(e) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(f) *Penicillin V content.* Accurately weigh approximately 50 milligrams of the sample, dissolve in absolute methanol, and make to 100 milliliters with absolute methanol. Determine the absorbance of the sample at the absorption peak at 276 mμ, using a suitable ultraviolet spectrophotometer and quartz cells. Set the instrument to 100-percent transmission with absolue methanol. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 240–290 mμ. If a nonrecording spectrophotometer is used, determine the absorbance (or a solution containing 20 milligrams per 100 milliliters) at the 276 mμ absorption peak, using a slit width of 0.5 millimeter or less. (The exact position of the peak should be determined for the particular instrument used.)

$$\text{Percent penicillin V} = \frac{\text{Absorbance at 276 m}\mu \times 100{,}000}{\text{Milligrams of sample (per 100 milliliters)} \times a_{vs}},$$

where:

a_{vs} = the absorptivity (1%, 1 cm.) of the penicillin V working standard similarly treated.

§ 141a.82 Penicillin V for oral suspension (phenoxymethyl penicillin V for oral suspension).

(a) *Potency.* Using the penicillin V working standard as the standard of comparison, proceed as directed in § 141a.48(a), except prepare the sample as follows: Reconstitute the product as directed in the labeling, remove a suitable representative aliquot, and dilute with sufficient 1 percent phosphate buffer, pH 6.0, to give a concentration of 2,000 units per milliliter (estimated) if the iodometric assay method is used, or 1.0 unit per milliliter (estimated) if the bioassay method is used. Its potency is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.26(e).

§ 141a.83 Benzathine penicillin V (benzathine penicillin V salt).

(a) *Potency.* Proceed as directed in § 141a.47(a), except use the penicillin V working standard as the standard of comparison.

(b) *Sterility.* Proceed as directed in § 141a.2, except prior to sterilization and 0.5 milliliter of polysorbate 80 to each tube of thioglycolate and Sabouraud's

medium, and after sterilization add sufficient penicillinase to each tube of media to completely inactivate the penicillin used in the test. During the period of incubation, shake the tubes at least once daily.

(c) *Pyrogens.* Proceed as directed in § 141a.3, except use sodium chloride solution as the diluent and inject 0.5 milliliter per kilogram of rabbit of a suspension containing 4,000 units per milliliter.

(d) *Toxicity.* Proceed as directed in § 141a.4, except use sodium chloride solution as the diluent and inject 0.25 milliliter of a suspension containing 4,000 units per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.26(e).

(f) *pH.* Proceed as directed in § 141a.5(b), using a saturated aqueous solution prepared by adding 5 milligrams per milliliter.

(g) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5(c).

(h) *Penicillin V content.* Using the spectrophotometric method, proceed as directed in § 141a.81(f), except that the calculations are as follows:

$$\text{Percent benzathine penicillin V} = \frac{\text{Absorbance at 276 m}\mu \times 100{,}000 \times 100}{\text{Milligrams of sample (in 100 milliliters)} \times a_{v_5} \times 69.2},$$

where:

a_{v_5} = absorptivity (1%, 1 cm.) of the penicillin V working standard similarly treated.
69.2 = percentage of penicillin V in pure benzathine penicillin V.

§ 141a.84 Tablets benzathine penicillin G and penicillin V.

(a) *Potency*—(1) *Total penicillin content.* Accurately weigh 6 tablets and grind them to a fine powder. Assay this powder by the iodometric method described in § 141a.5(d)(1), except in preparing the blank solution accurately weigh a portion of the powder equivalent to approximately 200,000 units of penicillin and make a suspension in 1-percent phosphate buffer, pH 6.0, with a volume of 100 milliliters. Shake well, pipette 2.0 milliliters into a 125-milliliter glass-stoppered Erlenmeyer flask, add 10.0 milliliters of 0.01 *N* iodine and immediately titrate with 0.01 *N* $NA_2S_2O_3$. In preparing the solution for inactivation, accurately weigh a portion of the powder equivalent to 200,000 units of penicillin and place in a 100-milliliter volumetric flask. Add 20 milliliters of 0.5 *N* NaOH and mix well. Allow to stand for 15 minutes, then add 10 milliliters of 1.2 *N* HC1, and make to volume with distilled water. Pipette a 2.0-milliliter aliquot into a 125-milliliter glass-stoppered Erlenmeyer flask and add 10.0 milliliters of 0.01 *N* iodine. Allow to stand for 15 minutes and then titrate the excess iodine with 0.01 *N* $Na_2S_2O_3$. Penicillin G is used as the standard of comparison. The total penicillin content is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(2) *Penicillin V content.* Place in a 125-milliliter separatory funnel an accurately weighed quantity of finely ground tablet powder equivalent to approximately 20 milligrams (33,900 units) of penicillin V. Add 50.0 milliliters of spectrophotometric grade chloroform and 1 milliliter of 1:4 H_3PO_4. Shake well for 2 minutes. Allow the layers to separate, filter the lower chloroform layer through a cotton pledget, and collect the clear chloroform solution. Determine the absorbance of the chloroform solution at the absorption peak at 276 mμ, using a suitable ultraviolet spectrophotometer and 1-centimeter quartz cells. Set the instrument to 100-percent transmission with chloroform. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 250–290 mμ. If a nonrecording spectrophotometer is used, the original sample used should be equivalent to approximately 10 milligrams of penicillin V. Determine the absorbance of the solution at the 276 mμ absorption peak. (The exact position of the peak should be determined for the particular instrument used.) Calculate the amount of penicillin V per tablet as follows:

$$\text{Penicillin V units per tablet} = \frac{\text{Absorbance at 276 m}\mu \times \text{average weight of each tablet} \times 1{,}695{,}000}{\text{Weight of powder taken} \times 2 \times a_{v_5}},$$

where:

a_{v_5} = absorptivity (1%, 1 cm.) of penicillin V working standard in chloroform, similarly treated.

The penicillin V content is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(3) *Penicillin G content.* The penicillin G content of the batch is the difference between the total penicillins determined by the method described in subparagraph (1) of this paragraph and the penicillin V content determined by the method described in subparagraph (2) of this paragraph. The penicillin G content is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.26 (e).

(c) *Disintegration time.* Proceed as directed in § 141a.9(c).

§ 141a.85 Capsules penicillin V.

(a) *Potency.* Using the pencillin V working standard as the standard of comparison, proceed as directed in § 141a.1, except prepare the sample as follows: Dissolve the contents of a representative number of capsules (usually 5 to 12) in sufficient redistilled methanol to give a concentration of not more than 50,000 units per milliliter, and further dilute with sufficient phosphate buffer, pH 6.0, to give a concentration of 2,000 units per milliliter (estimated) if the iodometric chemical assay is used, or 1.0 unit per milliliter (estimated) if the bioassay method is used. The average potency of capsules penicillin V is satisfactory if it is not less than 85 percent of the number of units per capsule that it is represented to contain.

(b) *Moisture.* Use the contents of 4 capsules and proceed as directed in § 141a.26 (e).

§ 141a.86 Procaine penicillin-streptomycin-polymyxin in oil; procaine penicillin-dihydrostreptomycin-polymyxin in oil; procaine penicillin-streptomycin-polymyxin ointment; procaine penicillin-dihydrostreptomycin-polymyxin ointment.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.8(a). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units per milliliter or per gram that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141b.129 (a) (1) of this chapter, except inactivate the penicillin in the combined extractives with sufficient penicillinase at 37° C. for 30 minutes. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter or per gram that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (2) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter or per gram that it is represented to contain.

(4) *Polymyxin content.* Proceed as directed in § 141b.112 (b) (1) of this chapter, with the following exceptions:

(i) In lieu of the directions for the preparation of the sample described in § 141b.112 (b) (1) (vii) of this chapter, prepare the sample by one of the following techniques:

(*a*) ***Extraction.*** Place a convenient-sized representative quantity of the sample in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake the sample and ether until homogeneous. Add 25 milliliters of 10-percent potassium phosphate buffer (pH 6.0) and shake. Remove the buffer layer and repeat the extraction with 25-milliliter portions of buffer at least three times and any additional times that may be necessary to insure complete extraction of the antibiotic. Combine the extractives. Inactivate the penicillin with sufficient penicillinase at 37° C. for 30 minutes. Make the proper estimated dilutions in 10-percent potassium phosphate buffer (pH 6.0) to give a concentration of 10 units per milliliter (estimated).

(*b*) ***Blending.*** Place a convenient-sized representative quantity of the sample in a blending jar containing 1.0 milliliter of polysorbate 80 and sufficient 1-percent phosphate buffer (pH 6.0) to give a final volume of 200 milliliters. If the sample consists of substantially more than 1 gram, use sufficient buffer to give a final volume of 500 milliliters. If the

concentration of polymyxin in the blend is less than 200 units per milliliter, 10-percent phosphate buffer (pH 6.0) should be used in lieu of 1-percent phosphate buffer (pH 6.0). Using a high-speed blender, blend the mixture for 2 minutes. Inactivate the penicillin with sufficient penicillinase at 37° C. for 30 minutes and make the proper estimated dilutions in 10-percent phosphate buffer (pH 6.0) to give a concentration of 10 units per milliliter (estimated).

(ii) The standard curve is prepared in the following concentrations: 6.4, 8.0, 10.0, 12.5, and 15.6 units per milliliter in 10-percent potassium phosphate buffer, pH 6.0. The 10 units per milliliter concentration is used as the reference point. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units per milliliter or per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b).

§ 141a.87 Benzathine penicillin V oral suspension; benzathine penicillin V for oral suspension.

(a) *Potency.* Use as the sample for assay a representative aliquot of the oral suspension; or if it is a dry mixture of the drug, use a representative aliquot of the drug reconstituted as directed in the labeling and proceed as directed in § 141a.47(a), except use the penicillin V working standard as the standard of comparison. Its potency is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *pH.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension or the suspension prepared as directed in the labeling of the drug.

(c) *Moisture (if it is the dry mixture of the drug).* Proceed as directed in § 141a.26 (e).

§ 141a.88 Benzathine penicillin G in streptomycin sulfate solution; benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary); potency, sterility, toxicity, pyrogens, pH.

Proceed as directed in § 141a.66 (a), (b), and (d).

§ 141a.89 Procaine penicillin-neomycin-polymyxin in oil; procaine penicillin-neomycin-polymyxin ointment.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.8(a). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units per milliliter or per gram that it is represented to contain.

(2) *Neomycin content.* Proceed as directed in § 141e.411 (a) (2) of this chapter, except that sufficient penicillinase is added to the sample under test to inactivate the penicillin. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter or per gram that it is represented to contain.

(3) *Polymyxin content.* Proceed as directed in § 141a.86(a)(4), except calculate from the quantity of neomycin found (using the method prescribed in subparagraph (2) of this paragraph) the quantity of neomycin that would be present when the sample is diluted to contain 10 units of polymyxin (labeled potency) per milliliter, and prepare the polymyxin standard curve by adding the calculated quantity of neomycin to each concentration of polymyxin used for the curve. Use the standard curve to calculate the polymyxin content of the sample. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units per milliliter or gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b).

§ 141a.90 Crystalline penicillin-streptomycin - polymyxin - oxytetracycline-carbomycin powder veterinary; crystalline penicillin-dihydrostreptomycin-polymyxin-oxytetracycline-carbomycin powder veterinary.

(a) *Potency*—(1) *Penicillin content.* Wash the contents of one immediate container of the sample into a 100-milliliter volumetric flask with approximately 70 milliliters of absolute methanol. Shake the mixture for 1 minute, dilute to 100 milliliters with absolute methanol, and mix thoroughly. Centrifuge a portion of this mixture to obtain a clear methanol solution. Dilute an aliquot of the clear solution with sufficient 1.0-percent phosphate buffer, pH 6.0, to obtain a concentration of 1.0 unit per milliliter (estimated) and proceed as directed in § 141a.1. Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Oxytetracycline content.* To an aliquot of the clear methanol solution prepared as directed in subparagraph (1) of this paragraph, add sufficient penicillinase to completely inactivate the penicillin and then dilute with sufficient 0.1 *M* monopotassium phosphate buffer, pH 4.5, to obtain a concentration of 0.24 microgram per milliliter (estimated) and proceed as directed in § 141c.218 (a) of this chapter, except use the oxytetracycline working standard (obtained from the U. S. P. Reference Standards Committee, 46 Park Avenue, New York 16, N. Y.) as the standard of comparison. Its content of oxytetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Carbomycin content.* To an aliquot of the clear methanol solution prepared as directed in subparagraph (1) of this paragraph, add sufficient penicillinase to completely inactivate the penicillin and then dilute with sufficient 0.1 *M* potassium phosphate buffer, pH 8.0, to obtain a concentration of 1.0 microgram per milliliter (estimated) and proceed as directed in paragraph (d) (1) of this section. Its content of carbomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(4) *Streptomycin content.* Using 10 milliliters of a freshly prepared 2-percent solution of anhydrous trichloroacetic acid in acetone, wash the contents of an immediate container of the sample into an extraction funnel prepared by fusing a ground-glass joint to the top of a medium porosity sintered-glass funnel (30 millimeters diameter). Shake the mixture for 1 minute and draw off the liquid under vacuum. Repeat the extraction with four 10-milliliter portions of a 2-percent solution of trichloroacetic acid in acetone and discard the filtrates. Wash the residue in the funnel with five 10-milliliter portions of 0.1 *M* potassium phosphate buffer (pH 8.0), withdrawing the washings with vacuum. Collect and combine the washings and dilute them to 50 milliliters with 0.1 *M* potassium phosphate buffer, pH 8.0. Proceed as directed in § 141b.101 (a) to (i) of this chapter. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(5) *Dihydrostreptomycin content.* Using the dihydrostreptomycin working standard as the standard of comparison, proceed as directed in subparagraph (4) of this paragraph. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(6) *Polymyxin content.* Dilute an aliquot of the buffer washings prepared as directed in subparagraph (4) of this paragraph with sufficient 10-percent potassium phosphate buffer, pH 6.0, to obtain a concentration of 10 units per milliliter (estimated). Proceed as directed in § 141b.112 (b) (1) of this chapter. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Oxytetracycline used in making the powder*—(1) *Potency.* Dilute the sample to be tested with sufficient 0.1 *N* HCl to give an appropriate stock solution. Further dilute with sufficient 0.1 *M* monopotassium phosphate buffer, pH 4.5, to obtain a concentration of 0.24 microgram per milliliter, and proceed as directed in § 141c.201 (a) (3) of this chapter, using the oxytetracycline working standard as the standard of comparison, except:

(i) Prepare the standard stock solution by dissolving an appropriate amount of the working standard in sufficient 0.1 *N* HCl to give a concentration of 1,000 micrograms per milliliter. This solution may be kept in the refrigerator for 1 week. Do not freeze.

(ii) To prepare solutions for the standard curve, make further dilution of the stock solution with 0.1 *M* monopotassium phosphate buffer, pH 4.5, to obtain concentrations of 0.148, 0.188, 0.240, 0.308, and 0.400 microgram per milliliter.

(2) *Moisture.* Proceed as directed in § 141a.5 (a).

(3) *Toxicity.* Proceed as directed in § 141a.4, using as a test dose 0.5 milliliter of an aqueous solution containing 2.0 milligrams per milliliter, prepared by dissolving 40 milligrams (as the anhydrous compound) in 2.0 milliliters of 0.1 *N* HCl (if it is the base) and diluting with the required amount of water.

(4) *pH.* Proceed as directed in § 141a.5 (b), using an aqueous solution containing 10 milligrams per milliliter.

(5) *Crystallinity.* Proceed as directed in § 141a.5 (c).

(d) *Carbomycin used in making the powder*—(1) *Potency*—(i) *Plate assay*—(a) *Cylinders (cups).* Use cylinders described under § 141a.1 (a)

(b) *Culture media.* Prepare the culture media for the base and seed layers and for carrying the test organism as directed in § 141a.1 (b) (1), except for the base and seed layers adjust the media to pH 8.0 after sterilization. Make the nutrient broth for preparing an inoculum of the test organism as directed in § 141a.1 (b) (3).

(c) *Working standard.* Keep the working standard at refrigeration in tightly stoppered vials, which in turn are kept in larger stoppered vials containing a suitable desiccant. Dry approximately 50 milligrams of the standard as described in § 141a.5 (a). Dissolve the weight of dry working standard in sufficient methyl alcohol to give a concentration of 10,000 micrograms per milliliter. Further dilute with sterile distilled water to give a stock solution of 100 micrograms per milliliter. This stock solution may be kept under refrigeration for 1 week. Make daily dilutions to a concentration of 1 microgram per milliliter using 0.1 *M* potassium phosphate buffer, pH 8.0.

(d) *Preparation of sample.* Prepare the sample to be tested by dissolving in a small amount of methyl alcohol and then further dilute in 0.1 *M* phosphate buffer, pH 8.0, to make an appropriate stock solution.

(e) *Preparation of suspension.* Proceed as directed in § 141d.301 (a) (5) of this chapter, except add 0.2 milliliter of the adjusted bulk suspension to 100 milliliters of agar that has been melted and cooled to 48° C.

(f) *Preparation of plates.* Proceed as directed in § 141d.301 (a) (6) of this chapter.

(g) *Assay.* Place six cylinders on the inoculated agar surface so that they are at approximately 60° intervals on a 2.8-centimeter radius. Use three plates for each sample. Fill three cylinders on each plate with the 1.0 microgram per milliliter standard and three cylinders with the sample diluted to 1.0 microgram per milliliter (estimated) in 0.1 *M* potassium phosphate buffer, pH 8.0, alternating standard and sample. At the same time, prepare a standard curve, using concentrations of the standard of 0.64, 0.80, 1.0, 1.25, and 1.56 micrograms per milliliter. Use three plates for the determination of each concentration on the curve except the 1.0 microgram per milliliter concentration, a total of 12 plates. The 1.0 microgram per milliliter concentration is the reference point of the curve. On each of three plates fill three cylinders with the 1.0 microgram per milliliter standard and the other three cylinders with the concentration of the standard under test. Thus there will be 36 of the 1.0 microgram determinations and nine determinations for each of the other points on the curve. Incubate the plates for 16 to 18 hours at 32° C. to 35° C. and measure the diameters of the circles of inhibition. Average the readings of the 1.0 microgram per milliliter concentrations and the readings of the concentration tested for each set of three plates and average also all 36 readings of the 1.0 microgram per milliliter concentration. The average of the 36 readings of the 1.0 microgram per milliliter concentration is the correction point for the curve. Correct the average value obtained for each concentration to the figure it would be if the average 1.0 microgram per milliliter reading for that set of three plates were the same as the correction point. Thus, if in correction of the 0.8 microgram concentration the average of the 36 readings of the 1.0 microgram concentration is 20.0 millimeters and the average of the 1.0 microgram concentration of this set of three plates is 19.8 millimeters, the correction is +0.2 millimeter.

If the average reading of the 0.8 microgram concentration of these same three plates is 19.0 millimeters, the corrected value is 19.2 millimeters. Plot these corrected values, including the average of the 1.0 microgram per milliliter concentration, on two-cycle semilogarithmic paper using the concentration in micrograms per milliliter as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Draw the standard curve through these points. To estimate the potency of the sample, average the zone readings of the standard and the zone readings of the sample on the three plates used. If the sample gives a larger zone size than the average of the standard, add the difference between them to the 1.0 microgram per milliliter unit zone on the standard curve. If the average value is lower than the standard value, subtract the difference between them from the 1.0 microgram per milliliter unit value on the curve. From the curves read the potencies corresponding to these corrected values of zone sizes.

(2) *Moisture.* Proceed as directed in § 141a.5 (a).

(3) *Toxicity.* Proceed as directed in § 141a.4, using as a test dose 0.5 milliliter of a solution containing 2 milligrams per milliliter.

(4) *pH.* Using an aqueous solution containing 10 milligrams per milliliter, proceed as directed in § 141a.5 (b).

(5) *Crystallinity.* Proceed as directed in § 141a.5 (c).

§ 141a.91 Hydrabamine penicillin V (penicillin V hydrabamine salt).

(a) *Potency.* Using the penicillin V working standard as the standard of comparison, proceed as directed in § 141a.75.

(b) *Toxicity.* Proceed as directed in § 141a.4, except use 0.5 percent gum arabic solution as the diluent and inject 0.25 milliliter of a suspension containing 4,000 units per milliliter.

(c) *Moisture.* Proceed as directed in § 141a.26 (e).

(d) *pH.* Proceed as directed in § 141a.5 (b), using a saturated aqueous solution prepared by adding approximately 5 milligrams per milliliter.

(e) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5 (c).

(f) *Hydrabamine absorptivity.* Place in a 125-milliliter separatory funnel an accurately weighed sample of approximately 100 milligrams. Add 20.0 milliliters of spectrophotometric grade chloroform and 20.0 milliliters of 0.5 *N* NaOH. Shake well for 1 minute. Allow the layers to separate, filter the lower chloroform layer through a cotton pledget, and collect the clear chloroform solution. Save the upper alkaline layer. Dilute 5.0 milliliters of the clear chloroform filtrate to 25.0 milliliters with spectrophotometric grade chloroform. Determine the absorbance of this chloroform solution at the absorption peak at 276 mμ, using a suitable ultraviolet spectrophotometer and quartz cells. Set the instrument to 100-percent transmission with chloroform. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 250–290 mμ. If a nonrecording spectrophotometer is used, 5.0 milliliters of the chloroform filtrate should be diluted to 50.0 milliliters with chloroform. Determine the absorbance of the solution at the 276 mμ absorption peak, using a slit width of 0.5 millimeter or less. (The exact position of the peak should be determined for the particular instrument used.) Calculate the hydrabamine absorptivity (1%, 1 cm.) as follows:

$$\text{Absorptivity} = \frac{\text{Absorbance at 276 m}\mu}{\text{Grams of sample per 100 milliliters}}$$

(g) *Penicillin V content.* Dilute 5.0 milliliters of the alkaline layer described in paragraph (f) of this section to 25.0 milliliters with distilled water. Determine the absorbance of the sample at the absorption peak at 276 mμ, using 0.1 *N* NaOH to set the instrument to 100-percent transmission. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 250–290 mμ. If a nonrecording spectrophotometer is used, dilute 5.0 milliliters of the alkaline layer to 50 milliliters with distilled water and determine the absorbance at the 276 mμ absorption peak.

$$\text{Percent hydrabamine penicillin V} = \frac{\text{Absorbance at 276 m}\mu \times 100{,}000 \times 100}{\text{Milligrams of sample (in 100 milliliters)} \times a_{ss} \times 54.0}$$

where:

a_{ss}=absorptivity (1%, 1 cm.) of the penicillin V working standard, similarly treated.
54.0=percentage of penicillin V in pure hydrabamine penicillin V.

§ 141a.92 Hydrabamine penicillin V oral suspension.

(a) *Potency.* Using the penicillin V working standard as the standard of comparison, proceed as directed in § 141a.76(a). Its potency is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(b) *pH.* Proceed as directed in § 141a.5 (b), using the undiluted aqueous suspension.

§ 141a.93 Penicillin-neomycin ointment.

(a) *Potency*—(1) *Total penicillin content; crystalline penicillin content; procaine penicillin content.* Proceed as directed in § 141a.35 (a) (1), (2), and (3).

(2) *Neomycin content.* Prepare the sample as directed in § 141a.8 (a), except use 0.10 *M* phosphate buffer, pH 8.0, and add sufficient penicillinase to inactivate the penicillin present. Proceed as directed in § 141e.410 (b) (1) of this chapter. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b).

§ 141a.94 Procaine penicillin-streptomycin-neomycin-erythromycin in oil; procaine penicillin-dihydrostreptomycin-neomycin-erythromycin in oil.

(a) *Potency*—(1) *Penicillin content.* Obtain the weight of the content of a syringe by weighing before and after ejecting the content into a beaker. Stir until homogeneous. Remove a representative sample (usually approximately 1.0 gram, accurately weighed) and place in a separatory funnel containing 50 milliliters of peroxide-free ether. Add 20 milliliters of potassium phosphate buffer (pH 8.0) and shake. Remove the buffer layer and repeat the extraction with three additional 20-milliliter portions of the buffer. Combine the buffer extracts and make to 100 milliliters with buffer. Place the buffer solution into a second separatory funnel and wash with three 30-milliliter portions of ether. Discard the ether washes. Remove an aliquot of the buffer solution and proceed as directed in § 141a.1 except § 141a.1 (d) and (i). If the iodometric chemical assay is used, proceed as directed in § 141a.5 (d) (1), except prepare the sample as directed in § 141a.35 (a) (1). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Using an aliquot of the buffer solution prepared in subparagraph (1) of this paragraph, proceed as directed in § 141b.101 (a) through (i) of this chapter, except add sufficient penicillinase to completely inactivate the penicillin present. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (2) of this paragraph, using the dihydrostreptomycin working standard as the standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(4) *Neomycin content.* Using an aliquot of the buffer solution prepared in subparagraph (1) of this paragraph, proceed as directed in § 141e.410(b) (1) of this chapter, except add sufficient penicillinase to completely inactivate the penicillin present. If Staphylococcus aureus is used as the test organism, use the Food and Drug Administration dihydrostreptomycin-resistant strain of Staphylococcus aureus (A.T.C.C. 6538–PR), which is grown and maintained on media containing 1,000 micrograms of dihydrostreptomycin per milliliter of agar. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(5) *Erythromycin content.* Proceed as directed in § 141b.126 (a) (1) (ii) of this chapter, except prepare the sample as follows: Place a representative sample (usually approximately 1.0 gram, accurately weighed) in a glass blending jar containing 100 milliliters of polyethylene glycol 400. Using a high speed blender, blend for 2 minutes and filter through a cotton plug or filter paper. Make an intermediate dilution of an aliquot of the filtrate with potassium phosphate buffer (pH 8.0) and add sufficient penicillinase to inactivate the penicillin present. Remove an aliquot and dilute with potassium phosphate buffer (pH 8.0) to give an erythromycin content of 1.0 μg. per milliliter (estimated). Its content of erythromycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.95 Penicillin-streptomycin-erythromycin ointment; penicillin-dihydrostreptomycin-erythromycin ointment.

(a) *Potency*—(1) *Penicillin content.* Obtain the weight of the content of a syringe by weighing before and after ejecting the content into a beaker. Stir until homogeneous. Remove a representative sample (usually approximately 1.0 gram, accurately weighed) and place in a separatory funnel containing 50 milliliters of peroxide-free ether. Add 20 milliliters of 0.1 *M* potassium phosphate buffer (pH 8.0) and shake. Remove the buffer layer and repeat the extraction with three additional 20-milliliter portions of the buffer. Place the buffer solution in a second separatory funnel and wash with three 30-milliliter portions of ether. Discard the ether washes. Remove an aliquot of the buffer solution and proceed as directed in § 141a.1, except § 141a.1 (d) and (i). If the iodometric chemical assay is used, proceed as directed in § 141a.5 (d) (1), except prepare the sample as directed in § 141a.35 (a) (1). Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Using an aliquot of the buffer solution prepared as directed in subparagraph (1) of this paragraph, proceed as directed in § 141b.101 (a) through (i) of this chapter, except add sufficieht penicillinase to completely inactivate the penicillin present. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (2) of this paragraph, using the dihydrostreptomycin working standard as the standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(4) *Erythromycin content.* Proceed as directed in § 141b.126(a) (1) (ii) of this chapter, except prepare the sample as follows: Place a representative sample (usually approximately 1.0 gram, accurately weighed), in a glass blending jar containing 99 milliliters of 0.1 *M* potassium phosphate buffer, pH 8.0, and 1 milliliter of polysorbate 80. Using a high-speed blender, blend for 2 to 3 minutes. Add 100 milliliters of 0.1 *M* potassium phosphate buffer, pH 8.0, and blend for an additional 2 to 3 minutes. Prepare an intermediate dilution by diluting an aliquot of the filtrate with 0.1 *M* potassium phosphate buffer (pH 8.0), and add sufficient penicillinase to inactivate the penicillin. Then further dilute with buffer to give an erythromycin content of 1.0 microgram per milliliter (estimated). Its content of erythromycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.96 Penicillin-streptomycin-neomycin-polymyxin ointment; penicillin-dihydrostreptomycin-neomycin-polymyxin ointment.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.35(a) (1), (2), and (3), except if diethylaminoethyl ester penicillin G hydriodide is used, after the extraction or blending procedure described in § 141a.8(a) (1) and (2), proceed as directed in § 141a.51(a), or if the iodometric assay is used, one drop of 1.2 *N* HCl is added to the blank immediately before the addition of the 0.01 *N* I_2. The penicillin content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141a.35 (a) (4). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in §141a.35 (a) (5). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(4) *Neomycin content.* Proceed as directed in § 141a.65 (a) (4). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number

of milligrams that it is represented to contain.

(5) *Polymyxin content.* Proceed as directed in § 141b.129(a)(3) of this chapter, except inactivate the penicillin with sufficient penicillinase at 37° C. for 30 minutes. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c).

§ 141a.97 Capsules penicillin-tetracycline phosphate complex-novobiocin-nystatin veterinary.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.21(a)(1)(i), except in lieu of the directions prescribed in § 141a.21(a)(1)(i)(*a*), prepare the stock solution by blending 3 capsules in 100 milliliters of potassium phosphate buffer, pH 8.0, using a glass jar and a high-speed blender. Its penicillin content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Novobiocin content.* Use a suitable aliquot of the stock solution prepared as directed in subparagraph (1) of this paragraph and proceed as directed in § 141a.21 (a) (2). Its content of novobiocin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Tetracycline phosphate complex content.* Proceed as directed in § 141c.231 (a) (1) of this chapter. Its potency is satisfactory if it contains the equivalent of not less than 85 percent of the number of milligrams of tetracycline hydrochloride that it is represented to contain.

(4) *Nystatin content.* Proceed as directed in § 141c.224 (a) (1) (ii) of this chapter. Its nystatin content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a).

§ 141a.98 Penicillin-streptomycin-bacitracin methylene disalicylate-neomycin ointment; penicillin-dihydrostreptomycin-bacitracin methylene disalicylate-neomycin ointment.

(a) *Potency*—(1) *Penicillin content.* Proceed as directed in § 141a.8(a). Its penicillin content is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141a.65(a)(2). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Dihydrostreptomycin content.* Proceed as directed in § 141a.65(a)(3). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(4) *Bacitracin methylene disalicylate content.* Proceed as directed in § 141a.49(a)(3). Its potency is satisfactory if it contains not less than 85 percent of the equivalent number of units of bacitracin that it is represented to contain.

(5) *Neomycin content.* Proceed as directed in § 141a.65(a)(4)(ii). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b).

§ 141a.99 Benzathine penicillin V for aqueous injection veterinary.

(a) *Potency.* Using the penicillin V working standard as the standard of comparison, proceed as directed in § 141a.48(a). Its potency is satisfactory if it contains not less than 90 percent of the number of units that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.83(b).

(c) *Pyrogens.* Proceed as directed in § 141a.83(c).

(d) *Toxicity.* Proceed as directed in § 141a.83(d).

(e) *Moisture (dry mixture of the drug).* Proceed as directed in § 141a.26 (e).

(f) *pH*—(1) *Dry mixture of the drug.* Proceed as directed in § 141a.5(b), using the suspension resulting when the amount of diluent recommended in the labeling is added.

(2) *Aqueous suspension of the drug.* Proceed as directed in § 141a.5(b), using the undiluted aqueous suspension.

§ 141a.100 Phenethicillin potassium (potassium α-phenoxyethyl penicillin).

(a) *Total potency.* Proceed as directed in § 141a.5(d)(1) except determine the factor F as the number of milliliters of 0.01 *N* I_2 absorbed by 1.0 milligram of the L-α-phenoxyethyl, penicillin potassium working standard.

$$\text{Units of phenethicillin potassium per milligram} = \frac{\text{Difference in titers} \times \text{potency of FDA L-α-phenoxyethyl, penicillin potassium working standard in units per milligram}}{\text{Milligrams in 2.0 ml. tested} \times F}$$

(b) *L-α-Phenoxyethyl, penicillin potassium content*—(1) *Microbiological activity of sample.* (i) Proceed as directed in § 141b.126 (a) (1) (ii) (*a*), (b), (e), and (f), of this chapter, except use 0.1 milliliter to 0.2 milliliter of the adjusted bulk suspension to 100 milliliters of agar for the inoculum.

(ii) *Working standard.* Dry the L-α-phenoxyethyl, penicillin potassium working standard as described in § 141a.5(a), and prepare a stock solution by dissolving a weighing of the dried standard in sufficient sterile distilled water to give a stock solution of 100 units per milliliter. This stock solution may be used for 1 week if stored in refrigerator.

(iii) *Standard curve.* Using the stock solution, further dilute with pH 7.8 to 8.0 buffer to get final concentrations of 0.064, 0.08, 0.1, 0.125, and 0.156 unit per milliliter, and proceed as described in § 141a.21(c)(1)(vii).

(iv) *Assay.* Dissolve a weighing of the sample in sufficient pH 7.8 to 8.0 buffer to give a convenient stock solution. Further dilute with buffer to give an estimated concentration equivalent to 0.1 unit per milliliter of the L-α-phenoxyethyl, penicillin potassium standard and then proceed as described in § 141a.21 (c)(1)(viii).

(v) *Stock solution.* Prepare a stock solution of the D-α-phenoxyethyl, penicillin potassium standard as described in paragraph (b)(ii) of this section. Further dilute this stock solution to an estimated activity equivalent to 0.1 unit per milliliter of the L-α-phenoxyethyl, penicillin potassium standard, and proceed as described in subdivision (iv) of this subparagraph.

(vi) *Calculation.* Calculate the L-α-phenoxyethyl, penicillin potassium content of the sample from the following equation:

$$\text{Percent L-α-phenoxyethyl, penicillin potassium} = \frac{(R-r)}{(1-r)} \times 100$$

where:

R = Units of L-α-phenoxyethyl, penicillin potassium equivalent (found per milligram of sample in microbial assay) / Units per milligram found in iodometric assay of sample

and

r = L-α-phenoxyethyl, penicillin potassium equivalent in units per milligram (of D-α-phenoxyethyl, penicillin potassium standard) / Potency in units per milligram of L-α-phenoxyethyl, penicillin potassium standard

(c) *Phenethicillin potassium content.* Accurately weigh approximately 50 milligrams of the sample, dissolve in water, add to a 100-milliliter volumetric flask and make to volume with water. Determine the absorbance at 268 mμ, using a suitable ultraviolet spectrophotometer and quartz 1-centimeter cells. Set the instrument at zero absorbance with distilled water. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 240 mμ to 290 mμ. If a nonrecording spectrophotometer is used, determine the absorbance (on a solution containing 20 milligrams per 100 milliliters) at the 268 mμ absorption peak, using a slit width of 0.5 millimeter or less. (The exact position of the peak should be determined for the particular instrument used.) Calculate the absorptivity, (*a*). Repeat the procedure, using the L-α-phenoxyethyl, penicillin potassium standard.

$$\text{Percent phenethicillin potassium} = \frac{a\ (\text{sample})}{a\ (\text{standard})} \times 100$$

(d) *Moisture.* Proceed as directed in § 141a.5(a).

(e) *Toxicity.* Proceed as directed in § 141a.4, except use sodium chloride solution as the diluent.

(f) *pH.* Proceed as directed in § 141a.5(b).

(g) *Crystallinity.* Proceed as directed in § 141a.5(c).

(h) *Identity.* Add 0.5 milliliter of a methyl alcohol solution containing 2.0 milligrams per milliliter to a test tube, and dry under a current of air. Add one drop of an aqueous chromotropic acid solution containing 10 milligrams per milliliter. Add two milliliters of sulfuric acid and heat in a glycerol bath at 150° C. for 3 to 4 minutes. An olive-green color is produced. (Penicillin V or its salts give a blue or purple color.)

§ 141a.101 Phenethicillin potassium (potassium α-phenoxyethyl penicillin) tablets.

(a) *Potency.* Use the iodometric assay procedure in § 141a.5(d), except use the L-α-phenoxyethyl, penicillin potassium standard as the standard of comparison, and prepare the sample as follows: Place 12 tablets in a mortar and add approximately 20 milliliters of 1 percent phosphate buffer at pH 6.0. Disintegrate the tablets by grinding with a pestle. Transfer with the aid of small portions of the buffer solution to a 500-milliliter volumetric flask and make to 500 milliliters by adding sufficient phosphate buffer. Make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. The sample may also be prepared as follows: Place 12 tablets in a blending jar and add thereto approximately 100 milliliters of a 500-milliliter quantity of 1 percent phosphate buffer at pH 6.0. After blending for 1 minute with a high-speed blender add the remainder of the 500 milliliters of buffer. Blend again for 1 minute and make the proper estimated dilutions in 1 percent phosphate buffer at pH 6.0. The average potency of phenethicillin potassium tablets is satisfactory if they contain not less than 85 percent of the number of units per tablet that they are represented to contain.

(b) *Moisture.* Use 4 tablets and proceed as directed in § 141a.5(a).

(c) *Disintegration time.* Proceed as directed in § 141a.9(c).

§ 141a.102 Phenethicillin potassium (potassium α-phenoxyethyl penicillin) for oral solution.

(a) *Potency.* Prepare the sample as directed on its labeling. Transfer an aliquot containing 200,000 units to a 100-milliliter volumetric flask, make to volume with 1 percent phosphate buffer at pH 6.0, and assay by the iodometric assay procedure in § 141a.5(d), except use the L-α-phenoxyethyl, penicillin potassium standard as the standard of comparison. Its potency is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.26(e).

§ 141a.103 Methicillin sodium.

(a) *Potency.* Use the methicillin sodium working standard as the standard of comparison, and proceed as directed in § 141a.1, except that:

(1) *Plate assay.* (i) Prepare a stock solution containing 1,000 micrograms per milliliter. Prepare the standard curve by further diluting this stock solution, using 1 percent phosphate buffer, pH 6.0, to final concentrations of 6.4, 8.0, 10.0, 12.5 and 15.6 micrograms per milliliter. The 10.0 micrograms per milliliter concentration is the reference concentration.

(ii) Determine the inoculum of the *Staphylococcus aureus* suspension to be used for the seed layer by adding varying volumes of the standardized suspension to 100-milliliter volumes of the seed agar. Run test plates with the different inocula and the methicillin sodium reference concentration. Select as the optimum inoculum the one that results in the clearest and best defined zones of inhibition (usually between 0.3 and 1.0 milliliter per 100 milliliters of seed agar).

(2) *Iodometric assay.* If the iodometric assay is used, use a solution containing 1.0 milligram per milliliter.

If it is packaged for dispensing, its potency is satisfactory if the container contains not less than 90 percent or more than 115 percent of the number of milligrams that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141a.2, adding sufficient penicillinase to inactivate the penicillin (approximately 6,000 Levy units of penicillinase per tube) in the test for bacteria.

(c) *Pyrogens.* Proceed as directed in § 141a.3, except use sodium chloride injection as the diluent and inject 1.0 milliliter per kilogram of a solution containing 20 milligrams per milliliter.

(d) *Toxicity.* Proceed as directed in § 141a.4, except use sodium chloride injection as the diluent and inject 0.5 milliliter of a solution containing 100 milligrams per milliliter.

(e) *Moisture.* Proceed as directed in § 141a.26(e).

(f) *pH.* Proceed as directed in § 141a.5(b), using an aqueous solution containing 10 milligrams per milliliter.

(g) *Crystallinity.* Proceed as directed in § 141a.5(c).

(h) *Methicillin content.* Place a 200-milligram sample in a 100-milliliter volumetric flask. Dissolve and make to volume with distilled water. Remove a 5-milliliter aliquot and dilute to 50 milliliters with distilled water. Determine the absorbance at 280 millimicrons, using a suitable ultraviolet spectrophotometer and quartz 1-centimeter cells. Set the instrument at zero absorbance with distilled water. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 250 millimicrons to 300 millimicrons. If a nonrecording spectrophotometer is used, determine the absorbance (on a solution containing 10 milligrams per 100 milliliters) at the 280-millimicron absorption peak. (The exact position of the peak should be determined for the particular instrument used.) Calculate the absorptivity, "*a*." Repeat the procedure, using the methicillin sodium standard.

$$\text{Percent methicillin content} = \frac{a(\text{sample})}{a(\text{standard})} \times 100$$

(i) *Identity.* Use the sample solution prepared as described in paragraph (h) of this section and determine the absorbancies at the absorption maximum at 280 millimicrons and at the absorption minimum at 264 millimicrons.

$$\frac{a(280\ \text{millimicrons})}{a(264\ \text{millimicrons})} = 1.30 \text{ to } 1.45$$

§ 141a.104 Sodium oxacillin.

(a) *Potency.* Use the sodium oxacillin working standard as the standard of comparison, and proceed as directed in § 141a.1, except:

(1) *Plate assay.* (i) Prepare a stock solution containing 1,000 micrograms per milliliter. Prepare the standard curve by further diluting this stock solution, using 1 percent phosphate buffer, pH 6.0, to final concentrations of 3.2, 4.0, 5.0, 6.25, and 7.8 micrograms per milliliter. The 5.0 micrograms per milliliter is the reference concentration.

(ii) Determine the inoculum of the Staphylococcus aureus suspension to be used for the seed layer by adding varying volumes of the standard suspension to 100-milliliter volumes of the seed agar. Run test plates with the different inocula and the sodium oxacillin reference concentration. Select as the optimum inoculum the one that results in the clearest and best defined zones of inhibition (usually between 0.3 milliliter and 1.0 milliliter per 100 milliliters of seed agar).

(2) *Iodometric assay.* If the iodometric assay is used, use a solution containing 1.0 milligram per milliliter.

(b) *Toxicity.* Proceed as directed in § 141a.4, except use sodium chloride injection as the diluent and inject 0.5 milliliter of a solution containing 20 milligrams activity per milliliter.

(c) *Moisture.* Proceed as directed in § 141a.26(e).

(d) *pH.* Proceed as directed in § 141a.5(b).

(e) *Crystallinity.* Proceed as directed in § 141a.5(c).

(f) *Sodium oxacillin content.* Accurately weight approximately 60 milligrams of sample, and transfer to a 100-milliliter volumetric flask. Dissolve and dilute the sample to the mark with distilled water. Pipette a 5.0-milliliter aliquot of the sample solution into a 22 x 200 millimeter test tube, and add 5 milliliters of 20 *N* NaOH. Mix the solutions, and place the tube in a boiling water bath for 60 minutes. Cool the tube, carefully add 10 milliliters of 6 *N* HCl, mix, and place the tube in the boiling water bath for 10 minutes. Position the tube in the bath so that the two liquid levels are the same. After heating, remove the tube from the bath, carefully agitate the contents of the tube, and cool to room temperature. Quantitatively transfer the contents of the tube to a 250-milliliter volumetric flask. Add approximately 200 milliliters of freshly boiled

and cooled distilled water, then 4.0 milliliters of 7.5 *N* NH_4OH, and dilute to volume with freshly boiled and cooled distilled water. Determine the absorbance on a suitable spectrophotometer at 235 millimicrons against a reagent blank. Run concurrently with the sodium oxacillin standard, and calculate as follows:

$$\frac{A \text{ sample} \times \text{mg. standard (anhydrous basis)}}{A \text{ standard} \times \text{mg. sample (anhydrous basis)}} \times 100 = \text{Percent sodium oxacillin}$$

(g) *Identity.* Use the sample solution prepared in paragraph (f) of this section and record the ultraviolet spectrum between 230 millimicrons and 260 millimicrons. It should be basically identical to that of the standard similarly treated.

§ 141a.105 Sodium oxacillin tablets.

(a) *Potency*—(1) *Plate assay.* Place a representative number of tablets (usually 3 to 12) in a blending jar and add approximately 200 milliliters of a 500-milliliter quantity of 1 percent phosphate buffer, pH 6.0. After blending for 1 minute with a high-speed blender, add the remainder of the 500 milliliters of buffer. Blend again for 1 minute, remove an aliquot, and make the proper estimated dilutions to 5.0 micrograms per milliliter in 1 percent phosphate buffer, pH 6.0. Follow the plate assay procedure given in § 141a.104.

(2) *Iodometric assay.* In lieu of the plate assay method described in subparagraph (1) of this paragraph, the potency may also be determined by using the iodometric assay described in § 141a.5(d) except prepare the sample as follows: Grind a representative number of tablets (usually 5 to 12), using a mortar and pestle. Dilute a weighed portion of the powder (approximately 30 milligrams) with 1 percent phosphate buffer at pH 6.0 to a concentration of approximately 1.0 milligram per milliliter.

The potency of sodium oxacillin tablets is satisfactory if they contain not less than 90 percent of the number of milligrams per tablet that they are represented to contain.

(b) *Moisture.* Use four tablets and proceed as directed in § 141a.26(e).

(c) *Disintegration time.* Proceed as directed in § 141a.9(c).

§ 141a.106 Sodium oxacillin capsules.

(a) *Potency.* Proceed as directed in § 141a.105. The average potency of the sodium oxacillin capsules is satisfactory if they contain not less than 90 percent of the number of milligrams per capsule that they are represented to contain.

(b) *Moisture.* Use the contents of 4 capsules and proceed as directed in § 141a.26(e).

§ 141a.107 Buffered methicillin sodium (buffered sodium-2,6-dimethoxyphenyl penicillin).

(a) *Potency*—(1) *Preparation of sample.* (i) Dissolve an accurately weighed portion of the drug in 1 percent phosphate buffer, pH 6.0, to obtain an appropriate stock solution for assay.

(ii) Reconstitute the drug as directed in the labeling of the finished product. Using a syringe and needle, transfer a representative aliquot of the drug equivalent to one dose to a 100-milliliter volumetric flask; make to volume with 1 percent phosphate buffer, pH 6.0

(2) *Assay.* Using the solutions described in subparagraph (1) of this paragraph, proceed as directed in § 141a.-103(a).

The micrograms per milligram potency of the weighed sample of the drug is corrected for the sodium citrate content.

(b) *Sterility, pyrogens, toxicity, moisture, pH, crystallinity, methicillin content, and identity.* Proceed as directed in § 141a.103 (b), (c), (d), (e), (f), (g), (h), and (i).

PART 141b—STREPTOMYCIN (OR DIHYDROSTREPTOMYCIN) AND STREPTOMYCIN- (OR DIHYDROSTREPTOMYCIN-) CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

Sec.

141b.101 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; potency.

141b.102 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; sterility.

141b.103 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; toxicity.

141b.104 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; pyrogens.

141b.105 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; histamine.

141b.106 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; moisture, pH, identity.

141b.107 Streptomycin ointment, dihyrostreptomycin ointment; potency.

141b.108 Dihydrostreptomycin sulfate, crystalline dihydrostreptomycin sulfate, dihydrostreptomycin hydrochloride.

141b.109 Streptomycin tablets; dihydrostreptomycin tablets.

141b.110 Streptomycin for topical use.

141b.111 Streptomycin sulfate solution; dihydrostreptomycin sulfate solution; crystalline dihydrostreptomycin sulfate solution.

141b.112 Streptomycin - polymyxin - bacitracin tablets.

141b.113 Streptomycin syrup; streptomycin in gel (streptomycin oral suspension); dihydrostreptomycin syrup; dihydrostreptomycin in gel (dihydrostreptomycin oral suspension).

141b.114 Streptomycin - bacitracin - polymyxin gauze pads.

141b.115 Streptomycin otic with antifungal agent; dihydrostreptomycin otic with antifungal agent.

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141b.116 Streptomycin - kaolin - pectin-aluminum hydroxide gel powder veterinary; dihydrostreptomycin - kaolin - pectin - aluminum hydroxide gel powder veterinary.

141b.117 Streptomycin for inhalation therapy; dihydrostreptomycin for inhalation therapy.

141b.118 Dihydrostreptomycin - streptomycin sulfates.

141b.119 Streptomycin sulfate veterinary; dihydrostreptomycin sulfate veterinary; dihydrostreptomycin hydrochloride veterinary.

141b.120 Streptomycin sulfate powder oral veterinary; streptomycin sulfate granules oral veterinary; dihydrostreptomycin sulfate powder oral veterinary; dihydrostreptomycin sulfate granule oral veterinary; dihydrostreptomycin hydrochloride powder oral veterinary; dihydrostreptomycin hydrochloride granules oral veterinary.

141b.121 Streptonicozid sulfate.

141b.122 Dihydrostreptomycin - streptomycin sulfates solution.

141b.123 Streptomycin - penicillin - sulfonamide with kaolin and pectin; dihydrostreptomycin - penicillin-sulfonamide with kaolin and pectin.

141b.124 Streptomycin hydrochloride solution oral veterinary; streptomycin sulfate solution oral veterinary.

141b.125 Dihydrostreptomycin - streptomycin sulfates with isonicotinic acid hydraside.

141b.126 Streptomycin-erythromycin ointment.

141b.127 Streptomycin - chlortetracycline-chloramphenicol-bacitracin dental cement; dihydrostreptomycin - chlortetracycline - chloramphenicol - bacitracin dental cement.

141b.128 Streptomycin-sodium sulfathiazole solution veterinary; dihydrostreptomycin-sodium sulfathiazole solution veterinary.

141b.129 Streptomycin-polymyxin-neomycin ointment; dihydrostreptomycin-polymyxin-neomycin ointment.

141b.130 Streptomycin - dihydrostreptomycin for inhalation therapy.

141b.131 Streptomycin-neomycin powder; dihydrostreptomycin - neomycin powder.

141b.132 Streptomycin solution for inhalation therapy veterinary: dihydrostreptomycin solution for inhalation therapy veterinary.

141b.133 Streptomycin-polymyxin in gel; dihydrostreptomycin - polymyxin in gel.

141b.134 Streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary.

141b.135 Streptomycin and para-aminobenzoic acid powder for inhalation therapy; dihydrostreptomycin and para-aminobenzoic acid powder for inhalation therapy.

141b.136 Streptomycin-polymyxin tablets; dihydrostreptomycin - polymyxin tablets.

141b.137 Streptomycin-neomycin for inhalation therapy veterinary; dihydrostreptomycin-neomycin for inhalation therapy veterinary.

141b.138 Dihydrostreptomycin - neomycin - polymyxin aerosol solution veterinary.

AUTHORITY: §§ 141b.101 to 141b.138 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 141b.101 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; potency.

(a) *Cylinders (cups).* Use cylinders described under § 141a.1(a) of this chapter.

(b) *Culture media.* Using ingredients that conform to the standards prescribed by the U. S. P. or N. F., make nutrient agar for the seed and base layers:

Beef extract	1.5 gm.
Yeast extract	3.0 gm.
Peptone	6.0 gm.
Agar	15.0 gm.
Distilled water q. s.	1,000.0 ml.

pH 7.8 to 8.0 after sterilization.

(c) *Working standard.* Keep the working standard (obtained from the Food and Drug Administration) at −20° C. in tightly stoppered containers which in turn are kept in larger stoppered vials containing a suitable desiccant. Dry an appropriate amount of the working standard as described in § 141a.5(a) of this chapter. Dissolve the weight of the dry working standard obtained in distilled water. Keep this stock solution in a refrigerator. Do not use it later than 30 days after it is made.

(d) *Standard curve.* Prepare daily in 0.10 *M* potassium phosphate buffer, pH 8.0, from the stock solution described in paragraph (c) of this section, concentrations of 0.64, 0.80, 1.0, 1.25, and 1.56 micrograms per milliliter solution. A total of 12 plates is used in the preparation of the standard curve, three plates for each solution except the 1.0 microgram per milliliter solution. The latter concentration is used as the reference point and is included on each plate. On each of three plates fill three cylinders with the 1.0 microgram per milliliter standard and the other three cylinders with the concentration under test. Thus there will be thirty-six 1-microgram determinations and nine determinations for each of the other points on the curve. After the plates have incubated, read the diameters of the circles of inhibition. Average the readings of the 1.0 microgram per milliliter concentration and the readings of the point tested for each set of three plates and average also all 36 readings of the 1.0 microgram per milliliter concentration. The average of the 36 readings of the 1.0 microgram per milliliter concentration is the correction point for the curve. Correct the average value obtained for each point to the figure it would be if the 1.0 microgram per milliliter reading for that set of three plates were the same as the correction point. Thus, if in correcting the 0.8-unit concentration, the average of the 36 readings of the 1.0 microgram per milliliter concentration is 16.5 millimeters and the average of the 1.0 microgram per milliliter concentration of this set of three plates is 16.3 millimeters, the correction is 0.2 millimeter. If the average readings of the 0.8 microgram per milliliter concentration of these same three plates is 15.9 millimeters, the corrected value is then 16.1 millimeters. Plot these corrected values, including the average of the 1.0 microgram per milliliter concentration, on 2-cycle semilog paper using the concentration in micrograms per milliliter as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Draw the standard curve through these points, either by inspection or by the equations in § 141a.1(h) of this chapter. The five points selected to determine the curve are arbitrary (they should be equally spaced) and should be so chosen that the limits of the curve will fill the needs of the laboratory. However, the potency of the sample under test should fall in the interval of from 64 percent to 156 percent of the correction point of the standard curve.

(e) *Preparation of sample.* Dissolve the sample to be tested in sufficient 0.1 *M* potassium phosphate buffer, pH 8.0, to make a convenient stock solution. Further dilute in buffer to a final concentration of 1.0 microgram per milliliter (estimated). Use this last dilution in the assay for potency.

(f) *Preparation of suspensions*—(1) *Preparation of spore suspensions.* The test organism is Bacillus subtilis (American Type Culture Collection 6633). Maintain the test organism on nutrient agar prepared as described in § 141a.1 (b) (1) of this chapter. Prepare a spore suspension by one of the following methods:

(i) Grow the organism for 1 week at 37° C. in a number of Roux bottles each containing 300 milliliters of nutrient agar prepared as described in § 141a.1 (b) (1) of this chapter. Suspend the spores in sterile distilled water and heat for 30 minutes at 65° C. Wash the spore suspension three times with sterile distilled water, heat again for 30 minutes at 65° C. and resuspend in sterile distilled water; or

(ii) Grow the organism for 5 days at 37° C. in a Roux bottle containing 300 milliliters of agar medium described in § 141a.1 (b) (1) of this chapter, but modified by the addition of 300 milligrams of $MnSO_4 \cdot H_2O$ per liter. Suspend the growth in 50 milliliters of sterile isotonic saline solution, centrifuge, and decant the supernatant liquid. Reconstitute the sediment and heat-shock the suspension by heating for 30 minutes at 70° C. Maintain the spore suspension at approximately 15° C. Determine by appropriate tests the quantity of spore suspension to be added to each 100 milliliters of agar for the secondary layer that will give sharp, clear zones of inhibition.

(2) *Preparation of vegetative suspension.* If a suspension of the test organism is to be used in lieu of the spore suspensions described in subparagraph (1) of this paragraph, prepare such suspension as follows: Using 2.0 milliliters of sterile distilled water, wash the organism from an agar slant (which has been incubated for 24 hours at 37° C.) onto the agar surface of a Roux bottle containing 300 milliliters of nutrient agar prepared as described in § 141a.1 (b) (1) of this chapter. Incubate for 24 hours at 37° C. Suspend the resultant growth in 50 milliliters of sterile distilled water and homogenize the suspension. Determine by appropriate tests the quantity of the vegetative suspension to be added to each 100 milliliters of agar for the secondary layer that will give sharp, clear zones of inhibition.

(g) *Preparation of plates.* Add 21 milliliters of agar described in paragraph (b) of this section to each Petri dish (20 by 100 millimeters). Melt the agar to be used for the secondary layer, cool to 55° to 60° C. and add the spore suspension prepared in paragraph (f) of this section. Mix thoroughly and add 4 milliliters to each of the plates containing the 21 milliliters of the uninoculated agar. Tilt the plates back and forth to spread the inoculated agar evenly over the surface.

(h) *Plate assay.* Place six cylinders on the inoculated agar surface so that they are at approximately 60° intervals on 2.8-centimeter radius. Use three plates for each sample. Fill three cylinders on each plate with the 1.0 mcg./ml. standard and three cylinders with the 1.0 mcg./ml. (estimated) sample, alternating standard and sample. Incubate the plates for 16 to 18 hours at 37° C. and measure the diameter of each circle of inhibition.

(i) *Estimation of potency.* Average the zone readings of the standard and average the zone readings of the sample on the three plates used. If the sample gives a larger average zone size than the average of the standard, add the difference between them to the 1.0 microgram zone size of the standard curve. If the average sample value is lower than the standard value, subtract the difference between them from the 1.0 microgram value on the curve. From the curve read the potencies corresponding to these corrected values of zone sizes.

(j) *Turbidimetric assay.* In lieu of the plate-assay method described in paragraph (h) of this section, the sample may be assayed for potency by the following method:

(1) Employ the agar described in paragraph (b) of this section (adjusted to a final pH of 7.0) for maintaining the test organism, which is Klebsiella pneumoniae (ATCC 10031), noncapsulated. Transfer stock cultures every week for test purposes. Transfer the organism to fresh agar slants and incubate overnight at 37° C. Suspend the growth from two or three of these slants in sterile distilled water and add approximately 5 milliliters of culture suspension to each of two Roux bottles containing the agar described in paragraph (b) of this section. Incubate the bottles overnight at 37° C., harvest the growth, using 50 milliliters of sterile distilled water per bottle, and pool the washings from the two bottles. Determine the dilution with water that will give a light transmission reading of 65 percent, using a filter of 6,500 Angstrom units in a photoelectric colorimeter. Keep the resulting suspension of organisms in the refrigerator and use for a period of not to exceed 1 week. Prepare a daily inoculum by adding 6.0 milliliters of the diluted suspension to each 100 milliliters of the nutrient broth prepared as directed in § 141a.1(b)(3) of this chapter, cooled to a temperature of approximately 15° C.

(2) *Working standard solutions.* Prepare the daily standard curve by diluting the stock solution described in paragraph (c) of this section in sterile distilled water to the following final concentrations: 23.9, 26.8, 30.0, 33.6 and 37.6

micrograms per milliliter. Add 1 milliliter of each final dilution to each of three tubes having an outside dimension of 16 millimeters x 125 millimeters. Add 9 milliliters of inoculated broth described in subparagraph (1) of this paragraph, to each tube and immediately place in a 37° C. water bath for 3 to 4 hours. After incubation, remove the tubes and add 0.5 milliliter of 12 percent formaldehyde to each tube.

(3) *Preparation of sample.* Dissolve the sample under test in sterile distilled water to prepare a convenient stock solution. Further dilute this stock solution in sterile distilled water to a final concentration of 30 micrograms per milliliter. Add 1 milliliter of this final concentration to each of three 16 millimeters x 125 millimeters tubes (outside dimensions). Add 9 milliliters of the inoculated broth described in subparagraph (1) of this paragraph to each tube and immediately place in a 37° C. water bath for 3 to 4 hours. (The sample tubes are placed in the water bath at the same time as the standard tubes.) After incubation, remove all tubes (sample and standard) and add 0.5 milliliter of 12 percent formaldehyde to each tube. Read the absorbance values of all tubes in a suitable photo-electric colorimeter, using a wavelength of 530 mμ. Set the instrument at zero absorbance, using clear, uninoculated broth prepared as described in § 141a.1(b)(3) of this chapter.

(4) *Estimation of potency.* Plot the average values for each concentration of the standard on 1-cycle semilogarithmic paper with absorbance on the arithmetic scale and concentrations on the logarithmic scale. Construct the best straight line through the points, either by inspection or by means of the equations described in § 141c.231(a)(1)(v) of this chapter. Average the absorbance values for the sample and read the streptomycin concentration from the standard curve. Multiply the concentration by appropriate dilution factors to obtain the streptomycin content of the sample tested.

(k) *Potency.* The potency of streptomycin is satisfactory, when assayed by the methods described in this section, if the immediate containers contain 90 percent of the number of grams they are represented to contain.

§ 141b.102 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; sterility.

Use the entire contents of single-dose containers or the equivalent of approximately 0.5 gram (activity) from each multiple-dose container, and proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

§ 141b.103 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; toxicity.

Proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of a solution containing 2 mg./ml.

§ 141b.104 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; pyrogens.

Proceed as directed in § 141a.3 of this chapter, using as a test dose 1.0 milliliter per kilogram of a solution containing 10 mg./ml.

§ 141b.105 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; histamine.

Use a healthy adult cat as the test animal. Determine weight and place under general anesthesia by employing sufficient (150 mg./kg.) sodium phenobarbital administered intraperitoneally. Surgically expose the right carotid separating it completely from all surrounding structures, including the vagus nerve, by blunt dissection and cannulate. Surgically expose the femoral vein. Start the recording kymograph and inspect the tracings for amplitude of excursion and relative stability of pressure. Determine the sensitivity of the animal by injecting into the femoral vein standard solutions of histamine made to contain the equivalent of 1.0 microgram of histamine base per milliliter. Make injections at not less than 5-minute intervals using doses of 0.05, 0.1, and 0.15 microgram of histamine base per kilogram. Repeat these injections, disregarding the first series of readings, until the drop given by equivalent doses of histamine is relatively uniform. The fall in blood pressure given by 0.1 mcg./kg. of histamine base (not less than 20 millimeters of mercury) is subsequently employed as the standard in testing samples. The histamine standard is supplied on request. Inject 3 mg./kg. of the sample of streptomycin per milliliter maintaining the five-minute injection schedule. If a significant drop is encountered the dose is repeated after the animal has been retested with the standard histamine. The animal may be used as long as it remains reasonably stable and responsive to histamine. The product is satisfactory if the fall in blood pressure obtained with 3 milligrams of streptomycin per kilogram of body weight is no greater than the fall obtained with 0.1 microgram of histamine base per kilogram of body weight. (Dogs may be substituted for cats in this test provided the ratio of the doses of streptomycin and histamine employed is the same.)

§ 141b.106 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride; moisture, pH, identity.

(a) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(b) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a solution with a concentration of 0.2 gm./ml.

(c) *Identity.* Using distilled water, dilute the sample to be tested to a concentration of approximately 1,000 micrograms per milliliter. To 5.0 milliliters of this solution, add 2.0 milliliters of 1*N* NaOH and heat in a boiling water bath for 10 minutes. Cool in ice water for 3 minutes and then acidify the solution by adding 2.0 milliliters of 1.2*N* HCl. Add 5.0 milliliters of 0.25 percent ferric chloride reagent, prepared as directed in § 141b.108(b)(1). A violet color appears.

§ 141b.107 Streptomycin ointment; dihydrostreptomycin ointment; potency.

(a) *Streptomycin content.* Proceed as directed in § 141b.101 except paragraphs (j) and (k) thereof, and in lieu of the directions in § 141b.101 (e), prepare the sample as follows: Accurately weigh the tube and contents and squeeze approximately 1.0 gram into a blending jar containing 50 milliliters of 0.10 *M* potassium phosphate buffer (pH 7.8 to 8.0). Reweigh the tube to obtain weight of ointment used in the test. Using a high-speed blender, blend the mixture for 3 minutes. Dilute an aliquot of the mixture to contain 100 micrograms of streptomycin base (estimated) per milliliter. Transfer 1.0 milliliter of this solution to a 100-milliliter flask and make up to volume with 0.10 *M* potassium phosphate buffer (pH 7.8 to 8.0). Use this last dilution in the assay for potency. The potency of streptomycin ointment is satisfactory if it contains not less than 85 percent of the number of micrograms of streptomycin base per gram it is represented to contain.

(b) *Dihydrostreptomycin content.* Proceed as directed in paragraph (a) of this section, using the dihydrostreptomycin working standard as a standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of micrograms of dihydrostreptomycin base per gram it is represented to contain.

§ 141b.108 Dihydrostreptomycin sulfate, crystalline dihydrostreptomycin sulfate, dihydrostreptomycin hydrochloride.

(a) *Potency.* Using the dihydrostreptomycin working standard as a standard of comparison, proceed as directed in § 141b.101. Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams that it is represented to contain.

(b) *Content of streptomycin sulfate or streptomycin hydrochloride*—(1) *Reagents.* (i) 10 percent ferric chloride stock solution. Dissolve 5 grams of $FeCl_3 6H_2O$ in 50 milliliters 0.1 *N* HCl.

(ii) 0.25 percent ferric chloride solution—Dilute 2.5 milliliters of 10 percent ferric chloride in 0.1 *N* HCl to 100 milliliters with 0.01 *N* HCl. Prepare the solution fresh daily.

(2) *Standard curve.* Keep the working standard (obtained from the Food and Drug Administration) at −20° C. in tightly stoppered containers which in turn are kept in larger stoppered vials containing a suitable desiccant. Dry an appropriate amount of the working standard at 100° C. and a pressure of 5 millimeters or less for 4 hours. Prepare a stock aqueous solution containing 1.0 milligram of streptomycin base per milliliter. Store this standard solution in a refrigerator and use for no longer than 2 weeks. Transfer 1.0, 2.0, 3.0, 4.0, and 5.0 milliliters of this standard solution and 10 milliliters of distilled water to each of six 25-milliliter volumetric

flasks. Add 9.0, 8.0, 7.0, 6.0, and 5.0 milliliters of distilled water to the five tubes, respectively, to give each a total volume of 10 milliliters. To each add 2.0 milliliters of 1 *N* NaOH and then heat the flasks in a boiling water bath for 10 minutes. Cool the flasks in ice water for 3 minutes and acidify the solutions with 2.0 milliliters of 1.2 *N* HCl. To each flask add 5.0 milliliters of 0.25 percent ferric chloride reagent, make to volume with distilled water, and mix thoroughly. Transfer the colored solutions to 2.0-centimeter absorption cells and measure the percent light transmission at 530 mμ in a suitable photoelectric colorimeter. Set the colorimeter at 100 percent light transmission for the zero concentration and then obtain the percent light transmission of the sample. Prepare a standard curve on semilog paper, plotting the percent light transmission on the logarithmic ordinate scale and the concentration of streptomycin base on the abscissa.

(3) *Procedure.* Dilute the contents of a vial or a sufficient amount of bulk material to give a concentration of approximately 20 milligrams per milliliter. From the amount of streptomycin obtained, calculate the percent streptomycin as follows:

$$\text{Percent streptomycin} = \frac{\text{Milligrams of streptomycin} \times 100}{\text{Milligrams of dihydrostreptomycin found in the sample used}}$$

(c) *Sterility.* Proceed as directed in § 141b.102.

(d) *Toxicity, pyrogens, histamine, moisture, pH, crystallinity.* Proceed as directed in §§ 141b.103, 141b.104, 141b.105, 141b.106, and 141a.5 (c) of this chapter.

§ 141b.109 Streptomycin tablets; dihydrostreptomycin tablets.

(a) *Potency*—(1) *Streptomycin content.* Using 12 tablets, proceed as directed in § 141b.101, except § 141b.101 (j) and (k), and in lieu of the directions in § 141b.101(e), prepare the sample as follows: Place the tablets in a glass blending jar containing 500 milliliters of 0.1 *M* potassium phosphate buffer, pH 8.0. Using a high-speed blender, blend for 3 to 5 minutes and then make the proper estimated dilutions in the buffer solution; except if it is a bolus, use three tablets and grind with a mortar and pestle before blending. The average potency of streptomycin tablets is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (1) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. The average potency of dihydrostreptomycin tablets is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141b.110 Streptomycin for topical use.

(a) *Potency.* Proceed as directed in § 141b.101, except paragraph (k) thereof. The potency of streptomycin for topical use is satisfactory if the immediate containers are represented to contain:

(1) Less than 500 milligrams and contain 85% or more of the number of milligrams so represented;

(2) More than 500 milligrams and contain 90% or more of the number of milligrams so represented.

(b) *Sterility, toxicity, pyrogens, histamine, moisture, pH.* Proceed as directed in §§ 141b.102 to 141b.106.

§ 141b.111 Streptomycin sulfate solution; dihydrostreptomycin sulfate solution; crystalline dihydrostreptomycin sulfate solution.

(a) If it is streptomycin sulfate solution, proceed as directed in §§ 141b.101, 141b.102, 141b.104, 141b.105, and 141b.106 (b) and (c), and for the toxicity test proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of a solution containing 1.5 milligrams per milliliter.

(b) If it is dihydrostreptomycin sulfate solution or crystalline dihydrostreptomycin sulfate solution, proceed as directed in § 141b.108, except in lieu of the directions in § 141b.108 (b) determine the streptomycin content as follows:

(1) *Preparation of standard.* Prepare a standard aqueous solution of the Food and Drug Administration streptomycin working standard containing 0.25 milligram of streptomycin base per milliliter. Transfer 1.0, 1.5, and 2.0 milliliter aliquots to test tubes (approximately 16 millimeters×150 millimeters). Add 1.0, 0.5, and 0 milliliter of distilled water to give a 2.0-milliliter volume.

(2) *Preparation of sample.* Dilute 1.0 milliliter of the dihydrostreptomycin sulfate solution to be tested (containing 250 to 500 milligrams of dihydrostreptomycin) to 25.0 milliliters in a volumetric flask. Transfer 2.0 milliliters to a test tube.

(3) *Blank.* Use 2.0 milliliters of distilled water.

(4) *Procedure.* To each tube containing 2.0 milliliters, add, in turn, 8.0 milliliters of 0.1 *N* NaOH (freshly prepared from 1 *N* NaOH), mix thoroughly, and immediately determine the optical density at 325 mμ in a suitable spectrophotometer. Set the spectrophotometer at 100-percent light transmission for the blank similarly treated. Return the solution to the test tube, heat in a boiling water bath for 10 minutes, cool in an ice bath for 3 minutes, and allow to come to room temperature. Determine the optical density at 325 mμ. The difference in reading before and after heating is the optical density of the aliquot. Prepare a standard curve. The concentration of streptomycin in the sample solution obtained directly from the standard curve times 1,250, divided by the number of milligrams of dihydrostreptomycin in the original dihydrostreptomycin solution, equals the percent of streptomycin.

§ 141b.112 Streptomycin-polymyxin-bacitracin tablets.

(a) *Tablets*—(1) *Potency*—(i) *Streptomycin content.* Using 12 tablets, proceed as directed in § 141b.109(a)(1). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(ii) *Polymyxin content.* Using 12 additional tablets, proceed as directed in paragraph (b) of this section. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(iii) *Bacitracin content.* Proceed as directed in § 141e.403(a) of this chapter, except use the test organism and prepare the standard curve as directed in § 141a.49(a)(2)(ii) of this chapter. Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

(b) *Polymyxin used in making the tablets*—(1) *Potency*—(i) *Cylinders (cups).* Use cylinders described under § 141a.1 (a) of this chapter.

(ii) *Culture medium.* Using ingredients that conform to the standards prescribed, if any, by the U. S. P. or N. F., make nutrient agar for the seed and base layers:

(*a*) *Base layer.*

Pancreatic digest of casein	17.0 gm.
Papaic digest of soybean	3.0 gm.
Sodium chloride	5.0 gm.
Dipotassium phosphate	2.5 gm.
Dextrose	2.5 gm.
Agar	20.0 gm.
Distilled water, q. s.	1,000.0 ml.
Final pH	7.3.

(*b*) *Seed layer.* For seed layer make the following changes in the medium described in (*a*) of this subdivision.

Agar	12.0 gm.
Tween 80 (add Tween 80 after boiling)	10.0 gm.
Final pH	7.3.

In lieu of preparing the medium from the individual ingredients as specified, it may be prepared from a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such medium. Minor modifications of the specified individual ingredients are permissible if the resulting medium possesses growth-promoting properties at least equal to the medium described.

(iii) *Working standard.* Weigh out a sufficient quantity of the working standard (obtained from the U.S.P. Reference Standards Committee, 46 Park Avenue, New York 16, N.Y.), dried as described in § 141a.5(a) of this chapter, and dissolve in 2.0 milliliters of distilled water, then add sufficient 10 percent potassium phosphate buffer, pH 6.0, to make a 1,000 units per milliliter stock solution. This solution may be used for 2 weeks if kept in refrigerator.

(iv) *Standard curve.* Prepare daily a standard curve as directed in § 141a.21 (c) (1) (vii) of this chapter, with the following exceptions: Using a solution

of the polymyxin working standard in 10 percent potassium phosphate buffer, pH 6.0, prepare volumetrically the following concentrations: 6.4, 8.0, 10.0, 12.5, and 15.6 units per milliliter in 10 percent potassium phosphate buffer, pH 6.0. The 10 units per milliliter concentration is used as the reference point.

(v) *Preparation of test organism.* The test organism is Brucella bronchiseptica (American Type Culture Collection 4617) which is maintained on agar described under subdivision (ii) (*a*) of this subparagraph. Inoculate a Roux bottle containing this agar, subdivision (ii) (*a*), from a stock slant and incubate 24 hours at 32° C.–35° C. Wash the growth into sterile distilled water and standardize the resulting organism suspension to 50-percent light transmission using a filter having a wave length of 6,500 A. Run test plates, and use in the assay the amount of inoculum per 10 milliliters of seed agar which gives (ca) 15.0-millimeter zones of inhibition against the test organism with the 100 units per milliliter solution of polymyxin. Make a new suspension every two weeks.

(vi) *Preparation of plates.* Using the agar described in subdivision (ii) of this subparagraph, prepare the plates as described in § 141b.101 (g), except allow the agar for the secondary layer to cool to 48° C.–50° C. before adding the inoculum. It is not necessary to refrigerate the plates.

(vii) *Assay.* Dissolve in sufficient sterile distilled water to give a concentration of 30,000 units (estimated) per milliliter. Add sufficient 10 percent potassium phosphate buffer, pH 6.0 to make an appropriate stock solution. Dilute further in sterile 10 percent potassium phosphate buffer, pH 6.0, to a final concentration of 10 units (estimated) per milliliter, and proceed as directed in § 141b.101 (h) and (i).

(2) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using 0.5 milliliter of a solution prepared by diluting the sample to approximately 1,200 units per milliliter with physiological salt solution.

§ 141b.113 Streptomycin syrup; streptomycin in gel (streptomycin oral suspension); dihydrostreptomycin syrup; dihydrostreptomycin in gel (dihydrostreptomycin oral suspension).

(a) *Potency*—(1) *Streptomycin content.* Proceed as directed in § 141b.101, except § 141b.101(k), and except that if it is in an oil base proceed as directed in § 141a.35 (a) (2) of this chapter. Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams of streptomycin that it is represented to contain.

(2) *Dihydrostreptomycin content.* Using dihydrostreptomycin working standard as the standard of comparison, proceed as directed in § 141b.101, except § 141b.101 (k), and except that if it is in an oil base proceed as directed in § 141a.35 (a) (3) of this chapter. Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams of dihydrostreptomycin that it is represented to contain.

§ 141b.114 Streptomycin-bacitracin-polymyxin gauze pads.

(a) *Potency.* Proceed as directed in § 141b.112(a) (1), except soak the sample for not less than 1 hour with frequent agitation.

(b) *Sterility.* Using individual pads proceed as directed in § 141b.102. This method will demonstrate only those organisms which are not susceptible to these concentrations of streptomycin, bacitracin, and polymyxin.

(c) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141b.115 Streptomycin otic with antifungal agent; dihydrostreptomycin otic with antifungal agent.

(a) *Potency.* Proceed as directed in § 141b.101, except paragraph (k) thereof, and if it is dihydrostreptomycin otic with antifungal agent use the dihydrostreptomycin working standard as a standard of comparison. Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams of streptomycin or dihydrostreptomycin per milliliter that it is represented to contain.

(b) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using the undiluted solution or suspension.

§ 141b.116 Streptomycin-kaolin-pectin-aluminum hydroxide gel powder veterinary; dihydrostreptomycin-kaolin-pectin-aluminum hydroxide gel powder veterinary.

(a) *Potency*—(1) *Streptomycin content.* Using 3.0 grams of the sample, proceed as directed in § 141b.101, except paragraph (k) of that section. Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams of streptomycin it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (1) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams of dihydrostreptomycin it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141b.117 Streptomycin for inhalation therapy; dihydrostreptomycin for inhalation therapy.

(a) *Potency*—(1) *Streptomycin content.* Proceed as directed in § 141b.101, except if it is packaged with inert gases proceed as follows: Use not less than 6 immediate containers. Place one-half the number of such containers in a suitable sharp freezing unit having a temperature not higher than —30° C. After freezing, cut open the containers and transfer the contents of each to a suitable beaker and allow gas to evaporate. After gas has evaporated, wash and dry the residue remaining in the container into the beaker with sterile distilled water, after which wash the entire contents of the beaker into a 500-milliliter volumetric flask and make to mark with sterile distilled water. Use an appropriate aliquot of each of these solutions and proceed as directed in § 141b.101 to determine the average total quantity of streptomycin in each container. Expel the drug from each of the remaining containers as directed in its labeling. After all gas (with drug) has been expelled, cut open the containers and place each in a large beaker containing 500 milliliters of sterile distilled water. Let stand for not less than 15 minutes, with frequent agitation. Remove an aliquot and proceed as directed in § 141b.101 to determine the quantity of streptomycin that remains in each container. The quantity of streptomycin expelled is determined by subtracting the average amount of the residue found from the average total amount contained in the containers. Its potency is satisfactory if it contains not less than 90 percent, or 85 percent if it is packaged with inert gases, of the number of milligrams of streptomycin that it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (1) of this paragraph, except use the dihydrostreptomycin working standard as a standard of comparison. Its potency is satisfactory if it contains not less than 90 percent, or 85 percent if it is packaged with inert gases, of the number of milligrams of dihydrostreptomycin that it is represented to contain.

(b) *Unless it is packaged with inert gases, toxicity, histamine, moisture, pH, streptomycin content (if it is dihydrostreptomycin), crystallinity (if it is crystalline dihydrostreptomycin).* Proceed as directed in §§ 141b.103, 141b.105, 141b.106, 141b.108 (b), and 141a.5 (c) of this chapter.

(c) *If it is packaged with inert gases, moisture.* Proceed as directed in § 141a.7 (c) of this chapter, but in lieu of the directions for preparing the sample in § 141a.7 (c) (3) of this chapter prepare the sample and calculate as follows: Freeze the container as described in paragraph (a) of this section. After freezing, open the container and remove a representative 10-milliliter aliquot. Place this sample in a dry titrating vessel, immediately add an excess of Karl Fischer reagent, and back-titrate with water-methanol solution until the endpoint is reached.

$$\text{Percent moisture} = \frac{(v_1 - V_2 f) \times e}{100}$$

§ 141b.118 Dihydrostreptomycin-streptomycin sulfates.

(a) *Potency.* Proceed as directed in § 141b.108(a). Its total potency is satisfactory if it contains not less than 90 percent of the combined number of milligrams of dihydrostreptomycin and streptomycin that it is represented to contain.

(b) *Content of streptomycin sulfate.* Proceed as directed in § 141b.108 (b), making appropriate dilutions so that the aliquot used for the colorimetric measurement contains 5.0 milligrams of streptomycin (estimated) and modify the calculations in accordance with the dilutions made. Its content of streptomycin is satisfactory if it contains not less than 45 percent and not more than 55 percent of the total potency as determined under paragraph (a) of this section.

(c) *Sterility, toxicity, pyrogens, histamine, moisture, pH.* Using the total potency of the sample for preparing dilutions and weighings, proceed as directed in §§ 141b.102, 141b.103, 141b.104, 141b.105, and 141b.106.

§ 141b.119 Streptomycin sulfate veterinary; dihydrostreptomycin sulfate veterinary; dihydrostreptomycin hydrochloride veterinary.

(a) *Potency.* If it is streptomycin sulfate veterinary, proceed as directed in § 141b.101. If it is dihydrostreptomycin sulfate veterinary or dihydrostreptomycin hydrochloride veterinary, proceed as directed in § 141b.101(j), using the dihydrostreptomycin working standard as the standard of comparison.

(b) *Toxicity.* Proceed as directed in § 141b.103.

(c) *Moisture.* Using a 1-gram sample, proceed as directed in § 141a.5 (a) of this chapter.

(d) *pH.* Proceed as directed in § 141b.106 (b).

(e) *Streptomycin content (if it is dihydrostreptomycin).* Proceed as directed in § 141b.108 (b).

§ 141b.120 Streptomycin sulfate powder oral veterinary; streptomycin sulfate granules oral veterinary; dihydrostreptomycin sulfate powder oral veterinary; dihydrostreptomycin sulfate granules oral veterinary; dihydrostreptomycin hydrochloride powder oral veterinary; dihydrostreptomycin hydrochloride granules oral veterinary.

(a) *Potency.* Proceed as directed in § 141b.101, except if it contains dihydrostreptomycin use the dihydrostreptomycin working standard as the standard of comparison. Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams of streptomycin or dihydrostreptomycin per gram that it is represented to contain.

(b) *Moisture.* Using a 1-gram sample, proceed as directed in § 141a.5 (a) of this chapter.

§ 141b.121 Streptonicozid sulfate.

(a) *Potency*—(1) *Streptomycin content.* Dilute the sample with hydrochloric acid solution pH 1.5 to 1,000 micrograms per milliliter (estimated streptomycin activity). Heat at 50° C. for 30 minutes, cool rapidly and proceed as directed in § 141b.101. The streptomycin potency of streptonicozid sulfate is satisfactory if the immediate containers contain 90 percent of the streptomycin activity they are represented to contain.

(2) *Isonicotinic acid hydrazide content*—(i) *Reagents.* (*a*) 0.1 *N* $KBrO_3$-KBr solution: Dissolve 3 grams of $KBrO_3$ and 15 grams of KBr in sufficient water to make 1,000 milliliters.

(*b*) Concentrated hydrochloric acid.

(*c*) 20-percent potassium iodide solution.

(*d*) 0.05 *N* $Na_2S_2O_3$ (accurately standardized against KIO_3).

(ii) *Preparation of sample.* Place an accurately weighed sample of approximately 250 milligrams or an aliquot of a solution containing 250 milligrams of streptonicozid sulfate into a 250-milliliter iodine flask. Add sufficient water to give a volume of 25 milliliters.

(iii) *Blank.* Add 25 milliliters of distilled water in a 250-milliliter iodine flask.

(iv) *Procedure.* To each iodine flask containing the sample and blank, add 25 milliliters of 0.1 *N* $KBrO_3$-KBr solution and 5 milliliters of concentrated HCl. Stopper the flasks, and place distilled water in the wells around the stopper. Allow the flasks to stand for 15 minutes at room temperature, and then add 5 milliliters of 20-percent potassium iodide solution to each flask. Titrate the liberated iodine with 0.05 *N* $Na_2S_2O_3$, using starch as an indicator.

(v) *Calculations.*

$$\text{Percent isonicotinic acid hydrazide} = \frac{(B-S)\times N\times 3429}{W}$$

where:

B = milliliters of $Na_2S_2O_3$ required for the blank.
S = milliliters of $Na_2S_2O_3$ required for the sample.
N = normality of the $Na_2S_2O_3$
W = milligrams of sample.

(b) *Absorptivity.* Accurately weigh approximately 100 milligrams of the sample; dissolve in distilled water, and make to 100 milliliters. Dilute a 5-milliliter aliquot of this solution to 100 milliliters, allow to stand at room temperature for 15 minutes, and, using a suitable spectrophotometer, determine the absorbance of the solution in a 1-centimeter cell at 260 mμ compared with distilled water as a blank.

$$\text{Absorptivity (1\%, 1 cm.)} = \frac{\text{Absorbance at 260 m}\mu\times 20{,}000}{\text{Milligrams of sample}}.$$

(c) *Toxicity.* Proceed as directed under § 141a.4 of this chapter, using as a test dose 0 5 milliliter of a solution containing 1,000 micrograms of streptomycin activity per milliliter.

(d) *Sterility.* Proceed as directed under § 141a.2 of this chapter, using the equivalent of approximately 0.5 gram streptomycin activity, except that neither penicillinase nor the control tube is used in the test for bacteria.

(e) *Pyrogens, histamine, moisture, pH, and crystallinity.* Proceed as directed under §§ 141b.104, 141b.105, 141b.106, and 141a.5 (c) of this chapter.

§ 141b.122 Dihydrostreptomycin-streptomycin sulfates solution.

(a) *Combined potency of dihydrostreptomycin and streptomycin; content of streptomycin.* Proceed as directed in § 141b.118 (a) and (b).

(b) *Sterility, toxicity, pyrogens, histamine.* Proceed as directed in §§ 141b.102, 141b.103, 141b.104, and 141b.105.

(c) *pH.* Using the undiluted solution, proceed as directed in § 141a.5 (b) of this chapter.

§ 141b.123 Streptomycin-penicillin-sulfonamide with kaolin and pectin; dihydrostreptomycin-penicillin-sulfonamide with kaolin and pectin.

(a) *Potency*—(1) *Streptomycin content.* Proceed as directed in § 141b.101. Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams of streptomycin it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (1) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams of dihydrostreptomycin it is represented to contain.

(3) *Penicillin content.* Proceed as directed in § 141a.1 of this chapter. Its potency is satisfactory if it contains not less than 90 percent of the number of units of penicillin it is represented to contain.

(b) *Moisture content.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *pH.* Prepare the suspension as directed in the labeling of the drug and proceed as directed in § 141a.5 (b) of this chapter.

§ 141b.124 Streptomycin hydrochloride solution oral veterinary; streptomycin sulfate solution oral veterinary.

(a) *Potency.* Proceed as directed in § 141b.101. Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams of streptomycin per milliliter that it is represented to contain.

(b) *Toxicity.* Proceed as directed in § 141b.103.

(c) *pH.* Proceed as directed in § 141b.106 (b).

§ 141b.125 Dihydrostreptomycin-streptomycin sulfates with isonicotinic acid hydrazide.

(a) *Total potency*—(1) *Preparation of sample*—(i) *Reagents*—(*a*) *Benzaldehyde.* Boiling point 75–76° C./16 millimeters;

(*b*) *Acetone.* Reagent grade.

(ii) *Apparatus.* An extraction funnel is prepared by fusing a ground-glass stopper to the top of a medium porosity sintered-glass filter funnel (30-millimeter diameter)

(iii) *Procedure.* The entire sample is quantitatively transferred to the funnel as follows: Pour the dry sample into the funnel. Wash any material remaining in the bottle with three 5.0-milliliter portions of benzaldehyde, placing the washings into the funnel. Stopper the funnel and shake occasionally for 3 minutes. Filter off the benzaldehyde by vacuum. Repeat the shaking with two more 15-milliliter portions of benzaldehyde, discarding all benzaldehyde filtrates. Wash the residue in the funnel with about 10 milliliters of acetone, discarding the acetone filtrate. Dissolve the streptomycin and dihydrostreptomycin in the funnel with about 25 milliliters of water and transfer the solution to a 500-milliliter volumetric flask. Wash the funnel with water and transfer the

washings to the volumetric flask. Finally, wash the funnel with water by filtering the water by vacuum and add the filtrate to the volumetric flask. Dilute the sample to 500 milliliters with distilled water, then proceed as directed in § 141b.101 (j), using the dihydrostreptomycin working standard as the standard of comparison. The total potency is satisfactory if it contains not less than 90 percent of the combined number of milligrams of dihydrostreptomycin and streptomycin that it is represented to contain.

(b) *Content of streptomycin sulfate.* Using an aliquot of the solution prepared as directed in paragraph (a) of this section, proceed as directed in § 141b.108 (b), making appropriate dilutions so that the aliquot ultimately used for the colorimetric measurement contains 5.0 milligrams of streptomycin (estimated), and modify the calculations in accordance with the dilutions made. Its content of streptomycin is satisfactory if it contains not less than 45 percent and not more than 55 percent of the total potency as determined under paragraph (a) of this section.

(c) *Isonicotinic acid hydrazide content.* Proceed as directed under § 141b.121 (a) (2).

(d) *Sterility, pyrogens, histamine, moisture, pH.* Using the total potency of the sample for preparing dilutions and weighings, proceed as directed in §§ 141b.102, 141b.104, 141b.105, and 141b.106.

(e) *Toxicity.* Proceed as directed under § 141a.4 of this chapter, using as a test dose 0.5 milliliter of a solution containing 1,000 micrograms of total activity per milliliter.

§ 141b.126 Streptomycin-erythromycin ointment.

(a) *Ointment*—(1) *Potency*—(i) *Streptomycin content.* Proceed as directed in § 141b.101 (a) through (i), except prepare the sample as follows: Place a representative quantity of the ointment (usually an entire container) in a blending jar containing approximately 225 milliliters of chloroform. Using a high-speed blender, blend the mixture for 3 minutes. Transfer the blended material to a large Buchner funnel (at least 10 centimeters in diameter) fitted with a highly retentive filter paper and attached to a vacuum line. Apply vacuum long enough to insure removal of chloroform from the filter cake. Place the filter cake and the paper in a blending jar containing 250 milliliters of 0.1 *M* phosphate buffer, pH 8.0, and blend for 10 minutes. Filter the blended material through a fast, porous, filter paper. Dilute the filtrate to obtain a solution for assay containing 1.0 microgram per milliliter. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(ii) *Erythromycin content—(a) cylinders (cups).* Use cylinders described under § 141a.1 (a) of this chapter.

(*b*) *Culture media.* Prepare the culture media for the base and seed layers and for carrying the test organism as directed in § 141a.1 (b) (1) of this chapter, except for the base and seed layers adjust the media to pH 8.0 after sterilization. Make the nutrient broth for preparing an inoculum of the test organism as directed in § 141a.1 (b) (3) of this chapter.

(*c*) *Working standard.* Keep the working standard (obtained from the U. S. P. Reference Standards Committee, 46 Park Avenue, New York 16, N. Y.) at refrigeration in tightly stoppered vials, which in turn are kept in larger stoppered vials containing a suitable desiccant. Dry 30 milligrams to 50 milligrams of the standard as described in § 141a.5 (a) of this chapter. Dissolve the weight of dry working standard in sufficient methyl alcohol to give a concentration of 10,000 micrograms per milliliter. Further dilute with 0.1 *M* potassium phosphate buffer, pH 7.8 to 8.0, to give a stock solution of 1,000 micrograms per milliliter. This stock solution may be kept under refrigeration for 1 week.

(*d*) *Standard curve.* Using the working-standard stock solution, prepare a standard curve as directed in § 141b.101 (d).

(*e*) *Preparation of spore suspension.* The test organism is Sarcina lutea (P. C. I. 1001). Maintain the test organism on slants of nutrient agar described in (*b*) of this subdivision and transfer to a fresh agar slant once a week. Prepare a suspension of the test organism as follows: Streak an agar slant heavily with the test organism. Wash the growth off in about 3 milliliters of nutrient broth described in (*b*) of this subdivision. Use the suspension so obtained to inoculate the surface of a Roux bottle containing 300 milliliters of the nutrient agar. Spread the suspension over the entire surface with the aid of sterile glass beads. Incubate for 24 hours at 26° C. Wash the growth from the agar surface with 20 milliliters of nutrient broth described in (*b*) of this subdivision. If an aliquot of this bulk suspension, when diluted with nutrient broth 1:10, gives a 10-percent light transmission in a suitable photoelectric colorimeter equipped with a filter having a wave length of 6,500 Angstrom units, it is satisfactory for use. It may be necessary to adjust the bulk suspension by dilution, so that an aliquot of the adjusted suspension diluted 1:10 gives 10-percent light transmission. (The adjusted bulk suspension only, and not the 1:10 dilution of it, is used in preparing the seed layer.) The bulk suspension may be used in the test for 2 weeks. Add 0.3 milliliter of the adjusted bulk suspension to 100 milliliters of agar described in (*b*) of this subdivision, which has been melted and cooled to 48° C.

(*f*) *Preparation of plates.* Add 21 milliliters of the agar prepared in (*b*) of this subdivision to each Petri dish (20 mm. x 100 mm.). Distribute the agar evenly in the plates and allow it to harden. Use the plates the same day they are prepared. Add 4.0 milliliters of the inoculum prepared under (*e*) of this subdivision to each plate, tilting the plates back and forth to spread the inoculated agar evenly over the surface.

(*g*) *Assay.* Place a representative quantity of the ointment (usually an entire container) in a blending jar and add sufficient methyl alcohol to give a volume of approximately 100 milliliters. Using a high-speed blender, blend the mixture for 2 to 3 minutes. Add 400 milliliters of 0.1 *M* potassium phosphate buffer, pH 8.0, and blend for 2 to 3 minutes. Dilute the mixture to 1.0 microgram per milliliter (estimated) using 0.1 *M* potassium phosphate buffer, pH 8.0, and proceed as directed in § 141b.101 (h) and (i), except that the incubation temperature is 32° C. to 35° C. The sample may also be prepared by placing a representative quantity of the ointment in a 1,000 milliliter volumetric flask. Add 50 milliliters of ethyl ether and shake until dissolved. Add approximately 200 milliliters of methyl alcohol and bring to the 1,000 milliliter mark using distilled water. Dilute the mixture to 1.0 microgram per milliliter (estimated), using 0.1 *M* potassium phosphate buffer, pH 8.0, and proceed as directed in § 141b.101 (h) and (i), except that the incubation temperature is 32° C. to 35° C. Its content of erythromycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(iii) *Moisture.* Proceed as directed in § 141a.7 (c) of this chapter.

(b) *Erythromycin used in making the ointment*—(1) *Moisture.* Proceed as directed in § 141a.26 (e) of this chapter. Use the value obtained to calculate the weighed samples used in this paragraph.

(2) *Potency.* Proceed as directed in paragraph (a) (1) (ii) of this section, except in the preparation of the solution of the sample dissolve 40 milligrams (as the anhydrous compound) in a small amount of methyl alcohol and then further dilute in 0.10 *M* potassium phosphate buffer, pH 8.0, to make a solution containing 1.0 microgram per milliliter (estimated).

(3) *Toxicity.* Proceed as directed in § 141d.305 (b) of this chapter, except administer orally to each mouse 1.0 milliliter of a suspension of the drug containing 30 milligrams per milliliter.

(4) *pH.* Using a saturated aqueous solution (100 milligrams per milliliter), proceed as directed in § 141a.5 (b) of this chapter.

(5) *Color-identity test.* Dissolve about 3 milligrams of the sample in 2 milliliters of acetone and add an equal volume of concentrated hydrochloric acid. A rapid color development takes place beginning with orange, changing to red, and finally resulting in a deep purple. Shake with 2 milliliters of chloroform. A portion of the purple color extracts into the chloroform layer.

§ 141b.127 Streptomycin-chlortetracycline-chloramphenicol-bacitracin dental cement; dihydrostreptomycin-chlortetracycline-chloramphenicol-bacitracin dental cement.

(a) *Potency*—(1) *Streptomycin or dihydrostreptomycin content*—(i) *Reagents.* (*a*) Sodium nitroprusside solution, 10 percent (w/v).

(*b*) Potassium ferricyanide solution, 10 percent (w/v).

(c) Sodium hydroxide solution, 10 percent (w/v).

(d) Oxidized nitroprusside solution. Mix equal volumes of the 10-percent sodium nitroprusside, 10-percent potassium ferricyanide, and 10-percent sodium hydroxide solutions in the order named. A deep-red color is formed which changes to a yellow green after standing at room temperature for approximately 15 minutes. Dilute 1.0 milliliter of this yellow-green solution with water to 100 milliliters and shake. This is the oxidized nitroprusside solution to be used in the test. It should be prepared fresh daily. Each of the 10-percent solutions described is stable for at least 2 months when stored in amber bottles.

(e) 0.3 percent piperidine in acetone.

(f) Aectone.

(ii) *Preparation of standard.* Prepare aqueous solutions of the working standards of streptomycin or dihydrostreptomycin containing 0.2 milligram per milliliter. Transfer 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, and 7.0 milliliter portions to small flasks. Add sufficient water to give each a 10-milliliter volume.

(iii) *Preparation of sample.* Place an accurately weighed portion of approximately 700 milligrams of the dental cement in a sintered-glass filter funnel and wash with three successive 5-milliliter portions of 0.3-percent piperidine in acetone. Remove any residual piperidine with two 5-milliliter portions of acetone and suck dry with vacuum. To the residue on the filter add 10 milliliters of distilled water and 10 milliliters of the oxidized nitroprusside solution. Shake, and after 6 minutes filter and read the color as directed below.

(iv) *Blank.* Use 10 milliliters of distilled water.

(v) *Procedure.* To each flask containing 10 milliliters of the standard and blank add 10 milliliters of the oxidized nitroprusside solution and allow the color to develop at room temperature for 6 minutes. Determine the optical density of each of the standard solutions and the sample at 490 millimicrons, using a suitable spectrophotometer. The blank is used to set the instrument to zero optical density. The orange-red color produced is stable for 30 minutes. Prepare a standard curve on coordinate graph paper, plotting the optical density on the ordinate scale and the concentration of streptomycin or dihydrostreptomycin base on the abscissa. For the sample, the optical density found is used to obtain the concentration of streptomycin or dihydrostreptomycin directly from the standard curve. To obtain the potency of the sample, multiply the concentration found by the appropriate factors in accordance with the dilutions made. Its content of streptomycin or dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Chlortetracycline content*—(i) *Reagents.* Mix 8 volumes of 20-percent (w/v) K_2HPO_4 with 1 volume of 20-percent (w/v) KH_2PO_4.

(ii) *Apparatus.* (a) A Coleman electronic photofluorometer (Model 12) or a similar instrument, equipped with filter b–1 for incident light and filter b–2 for emitted fluorescence.

(b) Matched 18 x 150-millimeter Pyrex test tubes.

(iii) *Preparation of standards.* (a) Prepare the fluorometric standard by dissolving 20 milligrams of U. S. P. quinine sulfate in 1 liter of 0.1 *N* H_2SO_4. Dilute 5 milliliters of this stock standard to 200 milliliters with 0.1 *N* H_2SO_4. Store these standards in the dark.

(b) Prepare solutions of the chlortetracycline hydrochloride working standard to contain 5, 10, and 20 micrograms per 10 milliliters.

(iv) *Procedure.* Using the diluted quinine standard, set the fluorometric reading at 35.0. Make a homogenous slurry of 500 milligrams of the dental cement in 500 milliliters of water. Place a 10-milliliter portion of the slurry in one of the matched test tubes and add 2.0 milliliters of the buffer reagent. Centrifuge for 3 minutes at 3,000 r. p. m. and immediately read the blank fluorescence of this solution. Stir the solution and heat on a steam bath for 5 minutes. Cool, and wipe the inside surface of the test tube with a swab of glass wool. Centrifuge for 5 minutes at 3,000 r. p. m. and read the fluorescence within 1 hour. Subtract the initial blank fluorescence reading. Calculate the chlortetracycline content by reference to a standard curve prepared by treating the chlortetracycline standard solutions in a similar fashion. It is not necessary to centrifuge the standard solutions. Its content of chlortetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Chloramphenicol content*—(i) *Reagents.* (a) Ethyl acetate.

(b) Sodium hydrosulfite.

(c) 0.1 *N* NaOH.

(d) 5-percent $NaNO_2$.

(e) Concentrated HCl.

(f) 5-percent ammonium sulfamate.

(g) 0.5-percent N(1-naphthyl) ethylenediamine dihydrochloride.

(ii) *Standard.* Prepare the standard by dissolving 20 milligrams of chloramphenicol working standard in 500 milliliters of water.

(iii) *Procedure.* Place 500 milligrams of the dental cement in a 50-milliliter volumetric flask and add 25 milliliters of ethyl acetate. Heat to boiling on a steam bath. Cool and dilute to mark with ethyl acetate. Centrifuge, and place 15 milliliters of the clear solution in a 100-milliliter volumetric flask. Evaporate to dryness on a steam bath with the aid of a stream of compressed air. Dissolve the residue in a 3-milliliter portion of 0.1 *N* NaOH, add 25 milligrams of sodium hydrosulfite, and let stand at room temperature for 15 minutes. Add 0.5 milliliter of 5-percent $NaNO_2$ and 5 to 10 drops of concentrated HCl. After 2 minutes, add 1 milliliter of ammonium sulfamate. Wait 2 minutes and add 0.5 milliliter of N(1-naphthyl) ethylenediamine dihydrochloride. Make to 100 milliliters and after 2 hours read the absorbance at 558 millimicrons in a 2-centimeter cell against a reagent blank, using a suitable spectrophotometer. To 4.0, 5.0, and 6.0 milliliter portions of the standard chloramphenicol solution add 3 milliliters of 0.1 *N* NaOH and proceed as above, beginning with the addition of 25 milligrams of sodium hydrosulfite. From the readings obtained plot a standard curve and calculate the quantity of chloramphenicol in the sample from the standard curve. Its content of chloramphenicol is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(4) *Bacitracin content.* Weigh 2 grams of the dental cement and transfer to a sintered-glass funnel of medium porosity. Wash the cement five times by shaking with 5-milliliter portions of acetone, using a filter flask and vacuum. Allow the vacuum to dry the residue. Discard the washings. Wash the residue five times by shaking with 5-milliliter portions of 1-percent phosphate buffer, pH 6.0, withdrawing each portion under vacuum. Combine the washings and add sufficient buffer to give a bacitracin concentration of 2 units per milliliter (estimated). Use a chromatographic column made by blowing a glass tube, measuring approximately 85 millimeters by 7 millimeters, into the bottom of a glass test tube measuring 100 millimeters by 15 millimeters. Draw the end of the column to a tip and place a plug of glass wool in the tip. Fill the column with a slurry of 6.5 grams of acid-washed alumina (chromatographic grade) and 1-percent phosphate buffer, pH 6.0. Allow the alumina to settle in the tube and the excess buffer to drain off. When the liquid level nearly reaches the top of the column of alumina, add the sample solution (containing 2 units per milliliter) dropwise from a dropping funnel at the same rate that the buffer is being released from the tip. Discard the first 30 milliliters of effluent. Collect the remainder of the sample, dilute an aliquot with buffer to give a final bacitracin concentration of 1 unit per milliliter (estimated), and assay by the method prescribed in § 141a.49 of this chapter. Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141b.128 Streptomycin-sodium sulfathiazole solution veterinary; dihydrostreptomycin-sodium sulfathiazole solution veterinary.

(a) *Potency.* Proceed as directed in § 141b.101(j), except if it contains dihydrostreptomycin use the dihydrostreptomycin working standard as a standard of comparison. Its content of streptomycin or dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Sterility, pyrogens, histamine, streptomycin content if it is dihydrostreptomycin.* Proceed as directed in §§ 141b.102, 141b.104, 141b.105, and 141b.111 (b).

(c) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of a solution containing 1.5 milligrams of streptomycin or dihydrostreptomycin per milliliter.

(d) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using the undiluted drug.

§ 141b.129 Streptomycin-polymyxin-neomycin ointment; dihydrostreptomycin-polymyxin-neomycin ointment.

(a) *Potency*—(1) *Streptomycin content.* Proceed as directed in § 141b.101 (a) through (i), inclusive, except prepare the sample in one of the following ways:

(i) *Extraction.* Place a convenient sized representative quantity of the sample in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake the sample and ether until homegenous. Add a 20-milliliter portion of 0.1 *M* potassium phosphate buffer, pH 8.0, and shake well. Remove the buffer layer and repeat the extraction with 20-milliliter portions of buffer at least three times and any additional times that may be necessary to insure complete extraction of the antibiotic. Combine the extractives and make the appropriate estimated dilutions in 0.1 *M* potassium phosphate buffer, pH 8.0.

(ii) *Blending.* Place a convenient sized representative quantity of the sample in a blending jar containing 1.0 milliliter of a 10-percent aqueous solution of polysorbate 80 and sufficient 0.1 *M* potassium phosphate buffer, pH 8.0, to give a volume of 200 milliliters. Using a high-speed blender, blend for 2 minutes and then make the appropriate estimated dilutions with buffer. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (1) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(3) *Polymyxin content.* Proceed as directed in § 141b.112 (b) (1) with the following exceptions:

(i) In lieu of the directions for the preparation of the sample described in subdivision (vii) of § 141b.112 (b) (1), prepare the sample as follows: Place a convenient sized representative quantity of the sample in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake the sample and ether until homogeneous. Add 25 milliliters of 10-percent potassium phosphate buffer, pH 6.0, containing 2 grams of K_2HPO_4 and 8 grams of KH_2PO_4 in each 100 milliliters, and shake. Remove the buffer layer and repeat the extraction with 25-milliliter portions of buffer at least three times and any additional times that may be necessary to insure complete extraction of the antibiotic. Combine the extractives and make the proper estimated dilutions in 10-percent potassium phosphate buffer pH 6.0, to give a concentration of 10 units per milliliter (estimated). If the sample contains a water-soluble base, accurately weigh a representative sample and place in a blending jar containing 1 milliliter of polysorbate 80 and sufficient 10 percent potassium phosphate buffer, pH 6.0, to give a final volume of 200 milliliters. Use a high-speed blender and blend the mixture for 2 minutes. Make the proper estimated dilutions, using 10 percent potassium phosphate buffer, pH 6.0.

(ii) The standard curve is prepared in the following concentrations: 6.4, 8.0, 10.0, 12.5, and 15.6 units per milliliter in 10 percent potassium phosphate buffer, pH 6.0. The 10 units per milliliter concentration is used as the reference point. Calculate from the quantity of neomycin found (using the method described in subparagraph (4) of this paragraph), the quantity of neomycin that would be present when the sample is diluted to contain 10 units of polymyxin (labeled potency) per milliliter. Prepare the polymyxin standard curve by adding the calculated quantity of neomycin to each concentration of polymyxin used for the curve. Use the standard curve to calculate the polymyxin content. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(4) *Neomycin content.* Proceed as directed in § 141e.410 (b) (1) of this chapter, with the following exceptions:

(i) In lieu of the directions for the preparation of the sample described in § 141e.410 (b) (1) (vii) of this chapter, prepare the sample as directed in subparagraph (1) (i) of this paragraph or by a blending technique as follows: Place a convenient sized representative quantity of the sample in a blending jar containing 1.0 milliliter of a 0.3-percent aqueous solution of dioctyl sodium sulfosuccinate and sufficient 0.1 *M* potassium phosphate buffer, pH 8.0, to give a volume of 200 milliliters. Using a high-speed blender, blend for 5 minutes and then make the appropriate estimated dilutions with buffer.

(ii) Use as the test organism the Food and Drug Administration dihydrostreptomycin- (and streptomycin-) resistant strain of Staphylococcus aureus (American Type Culture Collection 6538–PR) which is grown and maintained on media containing 1,000 micrograms of dihydrostreptomycin per milliliter of agar. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b) of this chapter.

§ 141b.130 Streptomycin-dihydrostreptomycin for inhalation therapy.

(a) *Potency*—(1) *Total potency.* Using the dihydrostreptomycin working standard as the standard of comparison, proceed as directed in § 141b.101 (j), except if it is packaged with inert gases prepare the sample as directed in § 141b.117 (a) (1). Its total potency is satisfactory if it contains not less than 90 percent of the combined number of milligrams of streptomycin and dihydrostreptomycin that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141b.118 (b). Its content of streptomycin is satisfactory if it contains not less than 45 percent and not more than 55 percent of the total potency as determined under subparagraph (1) of this paragraph.

(b) *Unless it is packaged with inert gases, toxicity, histamine, moisture, and pH.* Proceed as directed in § 141b.117 (b).

(c) *If it is packaged with inert gases, moisture.* Proceed as directed in § 141b.117 (c).

§ 141b.131 Streptomycin-neomycin powder; dihydrostreptomycin-neomycin powder.

(a) *Potency*—(1) *Streptomycin content.* Proceed as directed in § 141b.101 (a) through (i). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (1) of this paragraph, using the dihydrostreptomycin working standard as the standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(3) *Neomycin content.* Proceed as directed in § 141e.410 (b) (1) of this chapter. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141b.132 Streptomycin solution for inhalation therapy veterinary; dihydrostreptomycin solution for inhalation therapy veterinary.

(a) *Potency.* Proceed as directed in § 141b.101, except that if it contains dihydrostreptomycin use the dihydrostreptomycin working standard as the standard of comparison. Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams per milliliter that it is represented to contain.

(b) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted drug.

§ 141b.133 Streptomycin-polymyxin in gel; dihydrostreptomycin-polymyxin in gel.

(a) *Potency*—(1) *Streptomycin content.* Using a representative portion of the sample blended for 2 minutes in from 100 milliliters to 500 milliliters of distilled water, proceed as directed in § 141b.101 (a) through (i), inclusive. Its content of streptomycin is satisfactory if it is not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Dihydrostreptomycin content.* Using the dihydrostreptomycin working standard as the standard of comparison, proceed as directed in subparagraph (1) of this paragraph. Its content of dihydrostreptomycin is satisfactory if it is not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Polymyxin content.* Proceed as directed in § 141b.112 (b) (1), with the following exceptions:

(i) In lieu of the directions for the preparation of the sample as directed in § 141b.112 (b) (1) (vii), prepare the sample as follows: To a representative portion of the sample add 1 milliliter of polysorbate 80 and sufficient potassium phosphate buffer, pH 6.0 (containing 2 grams of K_2HPO_4 and 8 grams of KH_2PO_4 in each 100 milliliters), to give a volume of from 100 milliliters to 500 milliliters. Shake for not less than 10 minutes or blend in a high-speed blender for 2 minutes and then make the appropriate dilutions in 10 percent potassium phosphate buffer, pH 6.0, to give a concentration of 10 units per milliliter (estimated).

(ii) The standard curve is prepared in the following concentrations: 6.4, 8.0, 10.0, 12.5, and 15.6 units per milliliter in 10 percent potassium phosphate buffer, pH 6.0. The 10 units per milliliter concentration is used as the reference point.

Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units it is represented to contain.

(b) *pH.* Using the undiluted drug, proceed as directed in § 141a.5 (b) of this chapter.

§ 141b.134 Streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary.

(a) *Potency*—(1) *Total potency.* Using the dihydrostreptomycin working standard as the standard of comparison, proceed as directed in § 141b.101(j). Its total potency is satisfactory if it contains not less than 90 percent of the combined number of milligrams of streptomycin and dihydrostreptomycin that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141b.118 (b). Its content of streptomycin is satisfactory if it contains not less than 45 percent and not more than 55 percent of the total potency as determined under subparagraph (1) of this paragraph.

(b) *Moisture.* Using a 1-gram sample, proceed as directed in § 141a.5 (a) of this chapter.

§ 141b.135 Streptomycin and para-aminobenzoic acid powder for inhalation therapy; dihydrostreptomycin and paraaminobenzoic acid powder for inhalation therapy.

(a) *Potency*—(1) *Streptomycin content.* Proceed as directed in § 141b.117 (a) (1). Its content of streptomycin is satisfactory if it contains not less than 95 percent of the number of milligrams that it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in § 141b.117 (a) (2). Its content of dihydrostreptomycin is satisfactory if it contains not less than 95 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter, except if it is packaged with inert gases proceed as directed in § 141b.117 (c).

§ 141b.136 Streptomycin-polymyxin tablets; dihydrostreptomycin-polymyxin tablets.

(a) *Potency*—(1) *Streptomycin content.* Using 12 tablets, proceed as directed in § 141b.109(a) (1). Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Dihydrostreptomycin content.* Using the dihydrostreptomycin working standard as the standard of comparison, proceed as directed in subparagraph (1) of this paragraph. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Polymyxin content.* Using 12 tablets, proceed as directed in § 141b.112(b) (1). Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(c) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141b.137 Streptomycin-neomycin for inhalation therapy veterinary; dihydrostreptomycin-neomycin for inhalation therapy veterinary.

(a) *Potency*—(1) *Streptomycin content.* Proceed as directed in § 141b.101, except paragraph (j) of that section. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Dihydrostreptomycin content.* Proceed as directed in subparagraph (1) of this paragraph, using the dihydrostreptomycin working standard as the standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Neomycin content.* Proceed as directed in § 141b.131(a)(3) or § 141c.242 (a)(2) of this chapter. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141b.138 Dihydrostreptomycin-neomycin-polymyxin aerosol solution veterinary.

(a) *Potency.* (1) Using a separate graduate for each container to be tested, eject the drug as directed in its labeling. Measure the volume of each dose until the total contents are expelled. Remove appropriate aliquots and proceed as follows:

(i) *Dihydrostreptomycin content.* Using the dihydrostreptomycin working standard as the standard of comparison, proceed as directed in § 141b.101 (a) through (i). Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(ii) *Neomycin content.* Proceed as directed in § 141a.65(a)(4)(ii) of this chapter, except omit the extraction procedure. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(iii) *Polymyxin content.* Proceed as directed in § 141c.421(a)(3) of this chapter. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *pH.* Using the undiluted solution, proceed as directed in § 141a.5(b) of this chapter.

PART 141c—CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE- (OR TETRACYCLINE-) CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

Sec.

141c.201 Chlortetracycline hydrochloride.
141c.202 Chlortetracycline hydrochloride ointment, chlortetracycline calcium ointment, chlortetracycline calcium cream; tetracycline hydrochloride ointment (tetracycline hydrochloride in oil suspension); tetracycline ointment (tetracycline cream).
141c.203 Chlortetracycline troches; tetracycline hydrochloride troches.
141c.204 Chlortetracycline hydrochloride capsules; tetracycline hydrochloride capsules; tetracycline capsules; tetracycline phosphate complex capsules.
141c.205 Chloretracycline powder (chlortetracycline hydrochloride powder); tetracycline hydrochloride powder; tetracycline powder.
141c.206 Chlortetracycline ophthalmic; tetracycline hydrochloride ophthalmic.
141c.207 Chlortetracycline tablets (chlortetracycline hydrochloride tablets); tetracycline hydrochloride tablets; tetracycline tablets.
141c.208 Chlortetracycline otic; tetracycline hydrochloride otic.
141c.209 Chlortetracycline dental cones.
141c.210 Chlortetracycline dental paste.
141c.211 Chlortetracycline surgical powder (chlortetracycline hydrochloride surgical powder); tetracycline hydrochloride surgical powder.
141c.212 Chlortetracycline suppositories (chlortetracycline hydrochloride suppositories); tetracycline hydrochloride suppositories.
141c.213 Chlortetracycline gauze packing.
141c.214 Chlortetracycline dressing.
141c.215 Chlortetracycline with vasoconstrictor.
141c.216 Tetracycline hydrochloride-oleandomycin ointment.
141c.217 Chlortetracycline calcium syrup (chlortetracycline calcium oral drops); tetracycline syrup (tetracycline oral drops); tetracycline magnesium syrup (tetracycline magnesium oral drops).
141c.218 Tetracycline hydrochloride.
141c.219 Crude chlortetracycline oral veterinary.
141c.220 Tetracycline.
141c.221 Tetracycline hydrochloride for intramuscular use; tetracycline phosphate complex for intramuscular use.

Sec.
141c.222 Tetracycline hydrochloride oral suspension (tetracycline hydrochloride homogenized mixture); tetracycline phosphate complex oral suspension (tetracycline phosphate complex oral drops); tetracycline hydrochloride oral solution; tetracycline calcium oral suspension; tetracycline oral suspension.
141c.223 Chlortetracycline-neomycin-streptomycin-penicillin ointment; chlortetracycline-neomycin - dihydrostreptomycin - penicillin ointment; tetracycline hydrochloride - neomycin - streptomycin-penicillin ointment; tetracycline hydrochloride-neomycin-dihydrostreptomycin - penicillin ointment.
141c.224 Tetracycline hydrochloride-nystatin capsules; tetracycline phosphate complex-nystatin capsules.
141c.225 Tetracycline hydrochloride-nystatin tablets.
141c.226 Tetracycline and vasoconstrictor suspension.
141c.227 Chlortetracycline spray dressing (chlortetracycline hydrochloride spray dressing).
141c.228 Tetracycline hydrochloride-neomycin tablets.
141c.229 Tetracycline-nystatin oral suspension; tetracycline phosphate complex-nystatin oral suspension (tetracycline phosphate complex-nystatin oral drops).
141c.230 Chlortetracycline hydrochloride powder topical; tetracycline hydrochloride powder topical.
141c.231 Capsules tetracycline and oleandomycin phosphate; capsules tetracycline and triacetyloleandomycin; capsules tetracycline hydrochloride and oleandomycin phosphate; capsules tetracycline hydrochloride and triacetyloleandomycin.
141c.232 Tetracycline phosphate complex.
141c.233 Tetracycline-oleandomycin phosphate for oral suspension.
141c.234 Capsules tetracycline hydrochloride and novobiocin; capsules tetracycline phosphate complex and novobiocin.
141c.235 Tetracycline hydrochloride-oleandomycin phosphate for aqueous injection.
141c.236 Tetracycline-nystatin for oral suspension.
141c.237 Chlortetracycline-neomycin-streptomycin ointment; chlortetracycline - neomycin - dihydrostreptomycin ointment; tetracycline hydrochloride - neomycin - streptomycin ointment; tetracycline hydrochloride - neomycin - dihydrostreptomycin ointment.
141c.238 Tablets tetracycline hydrochloride and novobiocin.
141c.239 Tetracycline-novobiocin for oral suspension.
141c.240 Tetracycline - triacetyloleandomycin syrup (tetracycline-triacetyloleandomycin oral drops; tetracyclinetriacetyloleandomycin homogenized mixture); potency.
141c.241 Chlortetracycline seed.
141c.242 Tetracycline-neomycin complex powder topical; tetracycline hydrochloride - neomycin sulfate powder topical.
141c.243 Capsules tetracycline hydrochloride - triacetyloleandomycin-nystatin.
141c.244 Tetracycline hydrochloride-neomycin spray ointment topical.
141c.245 Tetracycline-triacetyloleandomycin for oral suspension.
Sec.
141c.246 Tetracycline hydrochloride-neomycin in oil suspension.
141c.247 Chlortetracycline hydrochloride impregnated surgical silk.
141c.248 Rolitetracycline.
141c.249 Rolitetracycline for intravenous use.
141c.250 Rolitetracycline for intramuscular use.
141c.251 Demethylchloretracycline hydrochloride.
141c.252 Capsules demethylchlortetracycline hydrochloride.
141c.253 Demethylchlortetracycline.
141c.254 Demethylchlortetracycline for oral suspension.
141c.255 Demethylchlortetracycline syrup (demethylchlortetracycline oral drops).
141c.256 Chlortetracycline hydrochloride in oil oral veterinary.
141c.257 Tetracycline-amphotericin B for oral syrup; tetracycline-amphotericin B for oral drops.
141c.258 Demethylchlortetracycline hydrochloride ointment.
141c.259 Demethychlortetracycline hydrochloride - nystatin capsules.
141c.260 Capsules tetracycline phosphate complex-amphotericin B.
141c.261 Tetracycline-novobiocin oral suspension (tetracycline-novobiocin oral drops; tetracycline-novobiocin syrup).
141c.262 Tetracycline-amphotericin B syrup; tetracycline-amphotericin B oral drops.
141c.263 Demethylchlotetracycline – nystatin for oral suspension.

AUTHORITY: §§ 141c.201 to 141c.263 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 141c.201 Chlortetracycline hydrochloride.

(a) *Potency*—(1) *Cylinders (cups).* Use cylinders described in § 141a.1(a) of this chapter.

(2) *Culture media.* Use the medium described in § 141a.1(b) (2) of this chapter for the seed layer and the base layer, except that the pH is adjusted to 5.8–6.0 after sterilization.

(3) *Working standard.* Accurately weigh a suitable quantity of the chlortetracycline hydrochloride working standard and dissolve in 0.01 *N* HCl to make an appropriate stock solution. Keep in a glass-stoppered flask and store in the refrigerator for not more than 1 week.

(4) *Preparation of sample.* Dissolve the sample to be tested in 0.01 *N* HCl to make an appropriate stock solution. Make the final dilution in 1 percent phosphate buffer, pH 4.5, to contain 0.10 microgram per milliliter (estimated).

(5) *Preparation of suspension.* The test organism is Bacillus cereus var. mycoides (ATCC 11778). Maintain the test organism on slants of nutrient agar prepared as described in § 141a.1(b) (1) of this chapter and transfer to fresh agar slants once a month, incubating overnight at 30° C. Streak several slants heavily with the test organism and incubate overnight at 30° C. Wash off the growth with approximately 5 milliliters of sterile distilled water onto the surface of a Roux bottle containing 300 milliliters of the nutrient agar. Spread the suspension over the entire agar surface with the aid of sterile glass beads. Incubate for 1 week at 30° C. Using 25 to 50 milliliters of sterile distilled water, wash the growth from the agar surface into a glass-stoppered Erlenmeyer flask. Heat-shock this suspension for 30 minutes at 65° C. Wash three times with sterile distilled water, centrifuging between each washing and then heat-shock for 30 minutes at 65° C. Resuspend in sterile distilled water and maintain in a refrigerator. This spore suspension may be kept for 1 month. Determine the percent of spore suspension that gives clear, sharp zones of adequate size after incubation with 0.10 microgram per milliliter of the test standard. Add the appropriate amount of the spore suspension to each 100 milliliters of the agar used for the seed layer, which has been melted and cooled to 48° C.

(6) *Preparation of plates.* Add 21 milliliters of the agar prepared as in subparagraph (2) of this paragraph to each Petri dish (20 millimeters x 100 millimeters). Distribute the agar evenly in the plates and allow it to harden. Use the plates the same day they are prepared. Add 4.0 milliliters of the inoculum as prepared in subparagraph (5) of this paragraph to each plate, tilting the plates back and forth to spread the inoculated agar evenly over the surface. Use porcelain covers glazed on the outside.

(7) *Assay.* Place six cylinders on the inoculated agar surface so that they are at approximately 60° intervals on a 2.8 centimeter radius. Use three plates for each sample. Fill three cylinders on each plate with the 0.10 microgram per milliliter standard and three cylinders with the 0.10 microgram per milliliter (estimated) sample, alternating standard and sample. At the same time prepare a standard curve using concentrations of the standard of 0.064, 0.080, 0.10, 0.125, and 0.156 microgram per milliliter in phosphate buffer, pH 4.5. A total of 12 plates are used in the preparation of this standard curve, three plates for each solution, except the 0.10 microgram per milliliter solution. The latter concentration is used as the reference point and is included on each plate. On each of three plates fill three cylinders with the 0.10 microgram per milliliter standard and the other three cylinders with the concentration of the standard under test. Thus, there will be thirty-six 0.10 microgram determinations and nine determinations for each of the other points on the curve. Incubate the plates for 16 to 18 hours at 30° C. and measure the diameter of each circle of inhibition. Average the readings of the 0.10 microgram per milliliter concentration and the readings of the point tested for each set of three plates and average also all 36 readings of the 0.10 microgram per milliliter concentration. The average of the 36 readings of the 0.10 microgram per milliliter concentration is the correction point for the curve. Correct the average value obtained for each point to the figure it would be if the 0.10 microgram per milliliter reading for that set of three plates were the same as the correction point. Thus, if in correcting the 0.08 microgram per milliliter concentration the average of the 36 readings of the 0.10 microgram per milliliter concentration is 18.0 millimeters and the average of the 0.10

microgram per milliliter concentration of this set of three plates is 17.8 millimeters, the correction is +0.2 millimeter. If the average reading of the 0.08 microgram per milliliter concentration of those same three plates in 17.0 millimeters, the corrected value is then 17.2 millimeters. Plot these corrected values, including the average of the 0.10 microgram per milliliter concentration on one-cycle semilog paper, using the concentration in micrograms per milliliter as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Construct the best straight line through the points, either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e}{5},$$

$$H=\frac{3e+2d+c-a}{5},$$

where:

L = calculated zone diameter for the lowest concentration of the standard curve.

H = calculated zone diameter for the highest concentration of the standard curve.

c = average value of 36 zone diameters of the 0.1 microgram per milliliter standards.

a, b, d, e = corrected zone diameters for the 0.064, 0.080, 0.125, and 0.156 microgram per milliliter standard solutions, respectively.

Plot the value obtained for L and H and connect the points with a straight line. Use three plates for each sample. Fill three cylinders on each plate with the standard 0.10 microgram per milliliter solution and three cylinders on each plate with the 0.10 microgram per milliliter (estimated) sample, alternating standard and sample. Incubate all plates, including those containing the standard curve, at 30° C. overnight, and measure the diameter of each circle of inhibition. To estimate the potency of the sample, average the zone readings of the standard and the zone readings of the sample on the three plates used. If the sample gives a larger zone size than the average of the standard, add the difference between them to the 0.10 microgram per milliliter zone on the standard curve. If the average sample value is lower than the standard value, subtract the difference between them from the 0.10 microgram per milliliter value on the curve. From the standard curve, read the potencies corresponding to these corrected values of zone sizes.

(8) *Turbidimetric assay.* In lieu of the plate-assay method described above, the sample may be assayed for potency by the following turbidimetric method:

(i) *Test culture and media.* The test organism is Staphylococcus aureus (ATCC 6538–P). Prepare a Roux bottle suspension of this organism as described in § 141a.1(e) of this chapter. This suspension may be used for 2 weeks if stored in the refrigerator. Prepare the daily inoculum by adding 10 to 20 milliliters of the standardized suspension dilution to each liter of broth prepared as in § 141a.1(b)(3) of this chapter.

(ii) *Working standard.* Prepare a stock solution by dissolving an appropriate aliquot of the standard in sufficient 0.01 *N* HCl to give a concentration of 1,000 micrograms per milliliter. Keep in a glass-stoppered flask and store in the refrigerator for not more than 1 week. Prepare solutions for the daily standard curve by diluting an aliquot of the stock solution in 0.1 *M* phosphate buffer, pH 4.5, to the following concentrations: 0.036, 0.047, 0.060, 0.077, and 0.099 microgram per milliliter. Place 1 milliliter of each concentration in each of three replicate tubes 16 millimeters x 125 millimeters (outside dimension). To each tube, add 9 milliliters of inoculated broth described in subdivision (i) of this subparagraph and place immediately in a water bath at 37° C. for 3 to 4 hours. Remove the tubes and add 0.5 milliliter of a 12 percent solution of formaldehyde to each tube.

(iii) *Preparation of sample.* Prepare an appropriate stock solution of the sample in 0.01 *N* HCl. Dilute further in pH 4.5 buffer to a final estimated concentration of 0.06 microgram per milliliter. Add 1 milliliter of this final concentration to each of three replicate tubes and proceed as described for the standard solution tubes in subdivision (ii) of this subparagraph. After incubation and the addition of formaldehyde to all tubes, including standard and sample tubes, read the absorbance values in a suitable photoelectric colorimeter, using a wavelength of 530 mμ. Set the instrument at zero absorbance with clear, uninoculated broth prepared as described in § 141a.1(b)(3).

(iv) *Estimation of potency.* Plot the average absorbance values for each concentration of the standard on one-cycle semilogarithmic graph paper with absorbance values on the arithmetic scale and concentrations on the logarithmic scale. Construct the best straight line through the points either by inspection or by means of the equations described in § 141c.231(a)(1)(v). Average the absorbance values for the sample and read the chlortetracycline concentration from the standard curve. Multiply the concentration by appropriate dilution factors to obtain the chlortetracycline content of the sample.

(9) *Chlortetracycline content.* Its potency is satisfactory if the immediate containers contain 85 percent of the number of grams they are represented to contain.

(b) *Sterility.* Using 40 milligrams from each container tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of an aqueous solution containing 2 milligrams per milliliter, except if it is intended for use solely in the manufacture of a veterinary drug for nonparenteral use, use a test dose of 0.4 milliliter of such solution.

(d) *Pyrogens.* Proceed as directed in § 141a.3 of this chapter, using a test dose of 1.0 milliliter per kilogram of an aqueous solution containing 5 milligrams per milliliter.

(e) *Histamine.* Proceed as directed in § 141b.105 of this chapter, using as a test dose 0.6 milliliter per kilogram of a solution containing 5 milligrams per milliliter prepared with the diluent recommended by the manufacturer in his labeling for the drug.

(f) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

(g) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(h) *Microscopical test for crystallinity.* Proceed as directed in § 141a.5(c) of this chapter.

§ 141c.202 Chlortetracycline hydrochloride ointment, chlortetracycline calcium ointment, chlortetracycline calcium cream; tetracycline hydrochloride ointment (tetracycline hydrochloride in oil suspension); tetracycline ointment (tetracycline cream).

(a) *Potency.* If it is tetracycline hydrochloride ointment or tetracycline ointment, proceed as directed in § 141c.218(a), and if it is chlortetracycline ointment proceed as directed in § 141c.201(a), except § 141c.201(a)(10), and in lieu of the directions in § 141c.201(a)(4) and (8)(iii) prepare the sample as follows: Place a representative portion of the sample (usually approximately 1.0 gram, accurately weighed) in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake ointment and ether until homogeneous. Shake with a 25-milliliter portion of 0.01*N* HCl. Remove the acid layer and repeat the extraction with three 25-milliliter quantities of 0.01*N* HCl. Combine the extracts and make the proper estimated dilutions in 0.1 *M* monopotassium phosphate buffer, pH 4.5. The sample may also be prepared by placing a representative portion of the sample (usually 1.0 gram, accurately weighed) in a glass blending jar containing 200 milliliters of 0.01*N* HCl. Using a high-speed blender, blend the mixture for approximately 3 minutes and make proper estimated dilutions in 0.1 *M* monopotassium phosphate buffer, pH 4.5. The potency is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b) of this chapter.

§ 141c.203 Chlortetracycline troches; tetracycline hydrochloride troches.

(a) *Potency.* If it is tetracycline hydrochloride proceed as directed in § 141c.218(a), and if it is chlortetracycline hydrochloride troches proceed as directed in § 141c.201(a), except § 141c.201 (a)(10), and in lieu of the directions in § 141c.201(a) (4) and (8)(iii) prepare the sample as follows: Place 12 troches in a glass blending jar containing 500 milliliters of 0.01 *N* HCl. Using a high-speed blender, blend for 3 to 5 minutes and then make the proper estimated dilutions in the buffer solution. The average potency of the troches is satisfactory if they contain not less than 85 percent of the number of milligrams they are represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141c.204 Chlortetracycline hydrochloride capsules; tetracycline hydrochloride capsules; tetracycline capsules; tetracycline phosphate complex capsules.

(a) *Potency.* Using 3 capsules of 250 milligrams or 5 capsules of 50 milligrams or 100 milligrams and 500 milliliters of 0.01 *N* HCl in the blender, proceed as directed in § 141c.203(a) if it is chlortetracycline. If it is tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex, use 500 milliliters of 0.1 *N* HCl, and proceed as directed in § 141c.218(a). If it contains vegetable oils, use 1 milliliter of polysorbate 80 and sufficient solvent to give 500 milliliters. The average potency of the drug is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

§ 141c.205 Chlortetracycline powder (chlortetracycline hydrochloride powder); tetracycline hydrochloride powder; tetracycline powder.

(a) *Potency.* Using a 3.0-gram sample or the entire contents of the immediate container for each determination, proceed as directed in § 141c.218(a), if it is chlortetracycline powder. If it is tetracycline powder, blend a 3.0-gram sample as directed in § 141c.203(a), or reconstitute in the immediate container as directed in the labeling of the drug. Transfer an appropriate aliquot of 1.0 milliliter to 5.0 milliliters to a 100-milliliter volumetric flask and make to mark with 0.1 *N* HCl. Withdraw an aliquot from the volumetric flask and dilute to 0.24 microgram per milliliter, using *M*/10 phosphate buffer at pH 4.5 and proceed as directed in § 141c.218(a). The average potency of the powder is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline or tetracycline hydrochloride or tetracycline per gram or per immediate container that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter,

§ 141c.206 Chlortetracycline ophthalmic; tetracycline hydrochloride ophthalmic.

(a) *Potency.* If it is tetracycline hydrochloride ophthalmic, proceed as directed in § 141c.218 (a); if it is chlortetracycline ophthalmic, proceed as directed in § 141c.201 (a). Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Sterility.* Proceed as directed in § 141a.2 of this chapter except that:

(1) Do not use penicillinase or the control tube in the test for bacteria.

(2) In lieu of the last sentence of § 141a.2 (b) of this chapter, the batch meets the requirements of the test for bacteria if no tube shows growth.

(3) In lieu of the last sentence of § 141a.2 (c) of this chapter, the batch meets the requirements of the test for molds and yeasts if no tube shows growth.

(d) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a solution prepared as directed in the labeling of the drug.

§ 141c.207 Chlortetracycline tablets (chlortetracycline hydrochloride tablets); tetracycline hydrochloride tablets; tetracycline tablets.

(a) *Potency.* Proceed as directed in § 141c.204(a). The average potency of the drug is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) or § 141a.26 (e) of this chapter.

(c) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141c.208 Chlortetracycline otic, tetracycline hydrochloride otic.

(a) *Potency.* If it is chlortetracycline proceed as directed in § 141c.201(a), and if it is tetracycline hydrochloride proceed as directed in § 141c.218 (a).

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141c.209 Chlortetracycline dental cones.

(a) *Potency.* Proceed as directed in § 141c.203(a). The average potency of the cone is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141c.210 Chlortetracycline dental paste.

(a) *Potency.* Proceed as directed in § 141c.203 (a), using an accurately weighed sample of approximately 2.0 grams and blend in 200 milliliters of 0.01 *N* HCl. The potency of chlortetracycline dental paste is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b) of this chapter.

§ 141c.211 Chlortetracycline surgical powder (chlortetracycline hydrochloride surgical powder); tetracycline hydrochloride surgical powder.

(a) *Potency*—(1) *Dry powder.* If it is chlortetracycline, proceed as directed in § 141c.201(a), and if it is tetracycline hydrochloride proceed as directed in § 141c.218(a). The potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride that it is represented to contain.

(2) *Powder packaged with inert gases.* Proceed as directed in § 141c.230 (a) (2). The potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride that it is represented to contain.

(b) *Sterility.* Use approximately 40 milligrams from each container, except that if it is packaged with inert gases, thoroughly cleanse the valve (do not flame) of each container to be tested with a suitable disinfectant and carefully spray approximately 40 milligrams into each tube. Proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used.

(c) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter, except that if it is packaged with inert gases proceed as directed in § 141b.117 (c) of this chapter.

§ 141c.212 Chlortetracycline suppositories (chlortetracycline hydrochloride suppositories); tetracycline hydrochloride suppositories.

(a) *Potency.* If they are tetracycline hydrochloride suppositories, proceed as directed in § 141c.218(a); and if they are chlortetracycline suppositories, proceed as directed in § 141c.201(a), except subparagraph (10) of that paragraph, and in lieu of the directions in subparagraphs (4) and (8)(iii) of § 141c.201(a) prepare the sample as follows: Place three suppositories into a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake the suppositories and ether until homogeneous. Shake with a 50-millileter portion of 0.01 *N* HCl. Remove the aqueous layer and repeat the extraction with three 50-milliliter quantities of 0.01 *N* HCl. Combine the extractives and centrifuge an aliquot at 2,000 r.p.m. for 5 minutes. Remove an aliquot of the supernatant and make the proper estimated dilutions in the buffer solution. The average potency of the suppository is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline or tetracycline hydrochloride that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141c.213 Chlortetracycline gauze packing.

(a) *Potency.* Using three packings, obtain the average weight and average linear length per packing. Assay three packings by dissolving each in 500 milliliters of 0.1 *N* HCl and allow to soak with frequent agitation for not less than 2 hours. Use aliquots of these solutions and proceed as directed in § 141c.201(a). Calculate the average potency per gram and per linear foot. The average potency of the gauze packing is satisfactory if it contains not less than 85 percent of the number of milligrams per gram and per linear foot it is represented to contain.

(b) *Sterility.* Using individual gauze packings, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141c.214 Chlortetracycline dressing.

(a) *Potency.* Using appropriate volumes of peroxide-free ether and 0.01 *N* HCl and individual dressings, or if it is a strip dressing an accurately weighed representative portion of approximately 1.5 grams, proceed as directed in § 141c.202(a).

(b) *Sterility.* Using approximately one-fourth of each individual dressing tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141c.215 Chlortetracycline with vasoconstrictor.

(a) *Potency.* Proceed as directed in § 141c.201(a).

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141c.216 Tetracycline hydrochloride-oleandomycin ointment.

(a) *Potency*—(1) *Tetracycline hydrochloride content.* Proceed as directed in § 141c.231(a)(1), except prepare the sample as directed in § 141c.202(a). Its content of tetracycline hydrochloride is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(2) *Oleandomycin phosphate content.* Proceed as directed in § 141c.231 (c) (1), except prepare the sample as follows: Place a representative sample (usually 1 gram, accurately weighed) in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake ointment and ether until homogeneous. Shake with a 25-milliliter portion of potassium phosphate buffer (pH 8.0). Remove the buffer layer and repeat the extraction with three 25-milliliter quantities of buffer. Combine the extractives and make the proper estimated dilutions in the buffer solution. The sample may also be prepared by placing an accurately weighed sample of approximately 1.0 gram in a glass blending jar containing 200 milliliters of the buffer solution. Using a high-speed blender, blend the mixture for approximately 3 minutes and make proper estimated dilutions in the buffer solution. Its content of oleandomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(3) *Oleandomycin base content.* Proceed as directed in § 141c.231 (c) (1), except prepare the sample as follows: Place an accurately weighed sample of approximately 4.0 grams in a glass blending jar containing 100 milliliters of ethanol. Using a high-speed blender, blend the mixture for approximately 3 minutes. Remove an appropriate aliquot and dilute to the reference concentration, using potassium phosphate buffer, pH 8.0. Its content of oleandomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b) of this chapter.

(c) *Oleandomycin base used in making the ointment*—(1) *Potency.* Dissolve the sample in sufficient ethanol to give a stock solution of 1,000 μg. per milliliter (estimated). Remove an appropriate aliquot and dilute to the reference concentration of 5.0 μg. per milliliter (estimated), using potassium phosphate buffer, pH 8.0, and proceed as directed in § 141c.231 (c) (1).

(2) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of a saline solution containing 8.0 milligrams per milliliter prepared by dissolving 40 milligrams in 2.0 milliliters of 0.1 *N* HCl and diluting with the required amount of sterile normal saline solution.

(3) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(4) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using an aqueous suspension containing 100 milligrams per milliliter.

(5) *Crystallinity.* Proceed as directed in § 141a.5 (c) of this chapter.

§ 141c.217 Chlortetracycline calcium syrup (chlortetracycline calcium oral drops); tetracycline syrup (tetracycline oral drops); tetracycline magnesium syrup (tetracycline magnesium oral drops).

(a) *Potency.* If it is chlortetracycline calcium syrup, proceed as directed in § 141c.201(a). If it is tetracycline syrup or tetracycline magnesium syrup, use a 1-milliliter aliquot of the sample and proceed as directed in § 141c.205(a). Blend for 5 minutes and proceed as directed in § 141c.218(a). Its potency is satisfactory if it contains not less than 85 percent of the equivalent number of milligrams of chlortetracycline or tetracycline hydrochloride per milliliter that it is represented to contain.

(b) *pH.* Using the undiluted sample, proceed as directed in § 141a.5(b) of this chapter.

(c) *Toxicity (if it is chlortetracycline calcium syrup or tetracycline magnesium syrup).* Administer orally, by means of cannula or other suitable device, to each of 5 mice, within the weight range of 18 grams to 25 grams, 0.5 milliliter containing 12.5 milligrams, except that if it contains analgesic substances or antihistaminics, administer 0.5 milliliter containing 6.25 milligrams. Dilute the preparation with sterile distilled water, if necessary, to contain the quantity of drug per 0.5 milliliter. If no animal dies within 48 hours, the sample is nontoxic. If one or more animals die within 48 hours, repeat the test with 5 unused mice weighing 20 grams (±0.5 gram) each; if all animals survive the repeat test, the sample is nontoxic.

§ 141c.218 Tetracycline hydrochloride.

(a) *Potency.* Use the tetracycline hydrochloride working standard as the standard of comparison, and proceed as directed in § 141c.201(a), except:

(1) Use 0.1 *N* HCl instead of 0.01 *N* HCl for the preparation of the standard stock solution and the sample stock solution.

(2) In the cylinder-plate assay:

(i) Further dilute the samples in 0.1 *M* phosphate buffer, pH 4.5, to an estimated final concentration of 1.0 microgram per milliliter instead of 0.10 microgram per milliliter; and

(ii) The final concentrations for the standard curve are 0.64, 0.8, 1.0, 1.25, and 1.56 micrograms per milliliter.

(3) In the turbidimetric assay:

(i) Further dilute the samples in 0.1 *M* phosphate buffer, pH 4.5, to an estimated final concentration of 0.24 microgram per milliliter instead of 0.06 microgram per milliliter; and

(ii) The final concentrations for the standard curve are 0.146, 0.187, 0.240, 0.308, and 0.395 microgram per milliliter.

The potency of tetracycline hydrochloride intended for use by injection is satisfactory if each immediate container contains not less than 90 percent of the tetracycline hydrochloride that it is represented to contain.

(b) *Sterility and toxicity.* Proceed as directed in § 141c.201 (b) and (c).

(c) *Pyrogens.* Proceed as directed in § 141a.3 of this chapter, using as a test dose 1.0 milliliter per kilogram of an aqueous solution containing 500 micrograms per milliliter.

(d) *Histamine, moisture, pH, and crystallinity.* Proceed as directed in § 141c.201 (e), (f), and (g) and § 141a.5 (c) of this chapter.

(e) *Absorptivity.* Dissolve approximately 40 milligrams on the anhydrous basis of the sample, accurately weighed, in approximately 150 milliliters of distilled water by mixing thoroughly. Dilute to exactly 250 milliliters with distilled water and mix thoroughly. Transfer a 10.0-milliliter aliquot of this solution to a 100-milliliter volumetric flask, add about 75 milliliters of distilled water and 5.0 milliliters of 5 *N* NaOH, and then make to 100 milliliters with water and mix thoroughly. Exactly 6 minutes after the addition of the NaOH, determine the absorbance of the solution at 380 mμ compared with distilled water as a blank. Use a suitable spectrophotometer for the absorbance measurements.

$$\text{Absorptivity (1\%, 1 cm.)} = \frac{\text{Absorbance at 380 m}\mu \times 25{,}000}{\text{Weight of sample in milligrams}}.$$

§ 141c.219 Crude chlortetracycline oral veterinary.

(a) *Potency.* Accurately weigh approximately 3.0 grams of the sample and place in a blending jar containing 200 milliliters of an acid-acetone solution prepared with 1 part 4 *N* HCl, 6 parts distilled water, and 13 parts acetone. Blend for 3 minutes. Using an aliquot of the liquid, make the proper estimated dilutions in *M*/10 monopotassium phosphate buffer pH 4.5, shake well, and proceed as directed in § 141c.201(a)(8). Its content of chlortetracycline is satisfactory if it contains not less than 85 percent of the number of grams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141c.220 Tetracycline.

(a) *Moisture.* Proceed as directed in § 141a.26(e) of this chapter. Use the value obtained to calculate the weighed samples used in paragraphs (b), (c), and (f) of this section to the anhydrous compound.

(b) *Potency.* Using 40 milligrams (as the anhydrous compound) of sample, proceed as directed in § 141c.218 (a).

(c) *Toxicity.* Proceed as directed in § 141b.103 of this chapter, using as a test dose 0.5 milliliter of an aqueous solution containing 2.0 milligrams per milliliter prepared by dissolving 40 milligrams (as the anhydrous compound) in 2.0 milliliters of 0.1 *N* HCl and diluting with the required amount of water.

(d) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using an aqueous suspension prepared by adding 10 milligrams per milliliter.

(e) *Crystallinity.* Proceed as directed in § 141a.5 (c) of this chapter.

(f) *Absorptivity.* Proceed as directed in § 141c.218(e), except dissolve 40 milligrams (as the anhydrous compound) in 2.0 milliliters 0.1 *N* HCl and dilute to 250 milliliters with distilled water.

§ 141c.221 Tetracycline hydrochloride for intramuscular use; tetracycline phosphate complex for intramuscular use.

(a) *Potency.* Reconstitute the sample as directed on the label or labeling. Using a suitable syringe, withdraw a one-dose aliquot and place in a 100-milliliter volumetric flask. Make to mark with 0.1 *N* HCl, and proceed as directed in § 141c.218(a). Its potency is satisfactory if the immediate container contains not less than 90 percent of the number of milligrams of tetracycline hydrochloride or tetracycline phosphate complex that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141c.201 (b).

(c) *Pyrogens.* Proceed as directed in § 141c.218 (c).

(d) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(e) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(f) *Histamine in the tetracycline phosphate complex used in making the batch.* Proceed as directed in § 141b.105 of this chapter, using as a test dose 0.6 milliliter of a solution containing 5 milligrams per milliliter prepared by dissolving 40 milligrams in 2.0 milliliters of 0.1 *N* HCl and diluting with the required amount of water.

§ 141c.222 Tetracycline hydrochloride oral suspension (tetracycline hydrochloride homogenized mixture); tetracycline phosphate complex oral suspension (tetracycline phosphate complex oral drops); tetracycline hydrochloride oral solution; tetracycline calcium oral suspension; tetracycline oral suspension.

(a) *Potency.* Transfer 1 milliliter of the well-shaken suspension to a suitable high-speed blender containing 500 milliliters of 0.1 *N* HCl. Blend for 5 minutes and proceed as directed in § 141c.218(a). Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams, or the equivalent number of milligrams, of tetracycline hydrochloride per milliliter that it is represented to contain.

(b) *Moisture.* If it is tetracycline hydrochloride oral suspension, tetracycline oral suspension, tetracycline hydrochloride oral solution, or tetracycline phosphate complex oral suspension, proceed as directed in § 141a.7 of this chapter.

(c) *pH.* If it is tetracycline hydrochloride oral solution or tetracycline calcium oral suspension, use the undiluted drug and proceed as directed in § 141a.5 (b) of this chapter.

§ 141c.223 Chlortetracycline-neomycin-streptomycin-penicillin ointment; chlortetracycline-neomycin-dihydrostreptomycin-penicillin ointment; tetracycline hydrochloride-neomycin-streptomycin-penicillin ointment; tetracycline hydrochloride-neomycin-dihydrostreptomycin-penicillin ointment.

(a) *Potency*—(1) *Penicillin content.* Place an accurately weighed sample of approximately 1 gram in an extraction funnel prepared by fusing a ground-glass joint to the top of a medium-porosity sintered-glass filter funnel (30-millimeter diameter). Wash with five 10-milliliter portions of warm iso-octane and draw off the ointment base under vacuum. Discard the iso-octane washings. Wash the residue with three 10-milliliter portions of chloroform and draw off under vacuum, combine the extracts, and make to mark in a 250-milliliter volumetric flask with absolute alcohol. Make the proper estimated dilutions in 1-percent phosphate buffer, at pH 6.0, and proceed as directed in § 141a.1 of this chapter. Its content of penicillin is satisfactory if it contains not less than 85 percent of the number of units per gram of ointment that it is represented to contain.

(2) *Chlortetracycline content.* Wash the residue in the funnel four times with 10-milliliter portions of 0.3 percent piperidine in acetone solution. Withdraw each washing under vacuum. Combine the four washings in a 100-milliliter volumetric flask and make to mark with 0.1 *M* monopotassium phosphate buffer, pH 4.5. The sample may also be prepared by placing a representative portion (usually 1.0 gram, accurately weighed) in a glass blending jar containing 199 milliliters of 0.01 *N* HCl and 1.0 milliliter of polysorbate 80. Using a high-speed blender, blend the mixture for 2 to 3 minutes and make proper estimated dilutions in 0.1 *M* monopotassium phosphate buffer, pH 4.5, adding sufficient penicillinase to inactivate the penicillin. Proceed as directed in § 141c.201(a)(8). Its content of chlortetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(3) *Tetracycline hydrochloride content.* Prepare the sample as directed in subparagraph (2) of this paragraph and proceed as directed in § 141c.218. Its content of tetracycline hydrochloride is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(4) *Neomycin content.* The residue remaining in the funnel after the extraction described in subparagraph (2) of this paragraph contains the neomycin and streptomycin or dihydrostreptomycin. Wash this residue five times, using 10-milliliter aliquots of 0.1 *M* phosphate buffer, pH 8.0, drawing each washing off under vacuum. Combine the washings in a 100-milliliter volumetric flask and make to mark with 0.1 *M* phosphate buffer, pH 8.0. Using an aliquot of this aqueous solution, proceed as directed in § 141a.65(a)(4) (i) or (ii) of this chapter. The content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(5) *Streptomycin content.* Using an aliquot of the aqueous solution prepared in subparagraph (4) of this paragraph, proceed as directed in § 141b.101(a) through (i) of this chapter. The content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(6) *Dihydrostreptomycin content.* Using an aliquot of the aqueous solution prepared in subparagraph (4) of this paragraph, and the dihydrostreptomycin working standard as a standard of comparison, proceed as directed in § 141b.101 (a) through (i) of this chapter. The content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141c.224 Tetracycline hydrochloride-nystatin capsules; tetracycline phosphate complex-nystatin capsules.

(a) *Capsules*—(1) *Potency*—(i) *Tetracycline hydrochloride content; tetracycline phosphate complex content.* Proceed as directed in § 141c.204(a) for tetracycline hydrochloride capsules and tetracycline phosphate complex capsules. Its potency is satisfactory if it contains the equivalent of not less than 85 percent of the number of milligrams of tetracycline hydrochloride that it is represented to contain.

(ii) *Nystatin content.* Prepare the sample for assay by placing a representative number of capsules in a blending jar with sufficient dimethylformamide (previously adjusted to pH 6.5±0.5 with concentrated H_2SO_4) to give a stock solution of convenient concentration. Blend for 2 minutes in a high-speed blender. Assay as directed in paragraph (b) of this section. Its content of nystatin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(iii) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(b) *Nystatin used in making the capsules*—(1) *Potency*—(i) *Cylinders (cups).* Use cylinders described in § 141a.1 (a) of this chapter.

(ii) *Culture media.* Use ingredients that conform to the standards, if any, prescribed by the U. S. P. or N. F.

(*a*) Make nutrient agar for carrying the organism and for preparing the inoculated agar plates as follows:

Peptone	9.4 grams.
Yeast extract	4.7 grams.
Beef extract	2.4 grams.
Sodium chloride	10.0 grams.
Dextrose	10.0 grams.
Agar	23.5 grams.
Distilled water to make	1,000 milliliters.

pH 6.0 to 6.2 after sterilization.

(*b*) Make nutrient broth for preparing an inoculum of the test organism:

Peptone	10 grams.
Dextrose	20 grams.
Distilled water to make	1,000 milliliters.

pH 5.6 to 5.7 after sterilization.

In lieu of preparing the media from the individual ingredients as specified, they may be prepared from a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such media. Minor modifications of the specified individual ingredients are permissible if the resulting media possess growth-promoting properties at least equal to the media described.

(iii) *Working standard.* Dry an appropriate amount of the working standard (obtained from the U.S.P. Reference Standards Committee, 46 Park Avenue, New York 16, New York) for 2 hours at 40° C. at a pressure of 5 millimicrons or less. Dissolve a weight of the dried standard in sufficient dimethylformamide to give a stock solution of convenient concentration (usually 1,000 units to 5,000 units per milliliter). This stock solution should be prepared simultaneously with the samples to be tested and should be used for 1 day only.

(iv) *Preparation of sample.* Dissolve the sample to be tested in sufficient dimethylformamide to give a nystatin concentration of 400 units per milliliter (estimated). Further dilute with 10 percent potassium phosphate buffer, pH 6.0, to 20 units per milliliter (estimated).

(v) The test organism is Saccharomyces cerevisiae (ATCC 9763 or ATCC 2601 (no vitamin requirement)), which is maintained on slants of agar described under subdivision (ii) (*a*) of this subparagraph and transferred once a week. After transfer, the culture is incubated at 37° C. for 24 hours and then kept refrigerated. Prepare the organism suspension by either of the following methods:

(*a*) Inoculate 100 milliliters of the broth medium described under subdivision (ii) (*b*) of this subparagraph with a loopful of growth from the agar slant. Incubate the broth for 16 to 18 hours at 37° C. This broth culture may be used for several weeks if kept refrigerated.

(*b*) Wash the organism from the agar slant with 3 milliliters of sterile physiological saline solution onto a large agar surface such as that provided by a Roux bottle containing 300 milliliters of the agar described in subdivision (ii) (*a*) of this subparagraph. Spread the suspension of organisms over the entire agar surface with the aid of sterile glass beads. Incubate for 24 hours at 37° C. and then wash the resulting growth from the agar surface with about 30 milliliters of sterile sodium chloride solution. This suspension may be used for several weeks if kept refrigerated. Run test plates to determine the quantity of this broth culture (usually about 2.5 milliliters) or saline suspension (usually about 0.1 milliliter) that should be added to each 100 milliliters of agar to give clear, sharp inhibitory zones of appropriate size.

(vi) *Preparation of plates.* Melt a sufficient amount of the agar described in subdivision (ii) (*a*) of this subparagraph, cool to 48° C., add the proper amount of the test organism as described above, and mix thoroughly. Add 8 milliliters of this inoculated agar to each Petri dish (100 millimeters x 22 millimeters, with flat bottom). Distribute the agar evenly in the plates, cover with porcelain covers glazed on the outside, and allow to harden. After the agar has hardened, place 6 cylinders on the agar surface so that they are at approximately 60° intervals on a 2.8-centimeter radius.

(vii) *Standard curve.* Dilute aliquots of the standard stock solution with dimethylformamide to give concentrations of 256, 320, 400, 500, and 624 units per milliliter. Dilute these solutions with 10 percent potassium phosphate buffer, pH 6.0, to make concentrations of 12.8, 16.0, 20.0, 25.0, and 31.2 units per milliliter, respectively. A total of 12 plates is used in the preparation of the standard curve, three plates for each solution, except the 20 units per milliliter solution. The latter concentration is used as the reference point and is included on each plate. On each of the three plates fill three cylinders with the 20 units per milliliter standard and the other three cylinders with the concentration of the standard concentration under test. Thus, there will be 36 twenty-unit determinations and nine determinations for each of the other concentrations on the curve. Incubate the plates for 16 to 18 hours at 37° C. and measure the diameter of each zone of inhibition. Average the readings of the 20 units per milliliter concentration and the readings of the concentration tested for each set of three plates, and average also all 36 readings of the 20 units per milliliter concentration. The average of the 36 readings of the 20 units per milliliter concentration is the correction point for the curve. Correct the average value obtained for each point to the figure it would be if the 20 units per milliliter reading for that set of three plates were the same as the correction point. Thus, if in correcting the 16 units per milliliter concentration the average of the 36 readings of the 20 units per milliliter concentration is 16.0 millimeters and the average of the 20 units per milliliter concentration of this set of three plates is 15.8 millimeters, the correction is +0.2 millimeter. If the average reading of the 15 units per milliliter concentration of those same three plates is 15.0 millimeters, the corrected value is then 15.2 millimeters. Plot these corrected values, including the average of the 20 units per milliliter concentration on two-cycle semilog paper, using the concentration in micrograms per milliliter as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Draw the standard curve through these points.

(viii) *Assay.* Use 3 plates for each sample. Fill three cylinders on each plate with the 20 units per milliliter standard and three cylinders with the 20 units per milliliter (estimated) sample, alternating standard and sample. Incubate the plates for 16 to 18 hours at 37° C. and then measure the diameter of each zone of inhibition. To estimate the potency of the sample, average the zone readings of the standard and the zone readings of the sample on the three plates used. If the sample gives a larger zone size than the average of the standard, add the difference between them to the 20 units per milliliter zone on the standard curve. If the average value is lower than the standard value, subtract the difference between them from the 20 units per milliliter value on the curve. From the curves read the potencies corresponding to these corrected values of zone sizes.

(ix) *Turbidimetric assay*—(*a*) *Test culture and media.* Maintain the test organism Saccharomyces cerevisiae (ATCC 9763) as described in subdivision (v) of this subparagraph. For use in the assay, prepare an organism suspension as directed in subdivision (v) (*a*) of this subparagraph. Adjust this stock suspension, so that a 1:10 dilution in the nutrient broth will have an absorption of 0.350 at a wavelength of 650 mμ, using a suitable photoelectric colorimeter and an 18-millimeter diameter test tube as an absorption cell. Prepare the inoculated broth by adding from 3 milliliters to 5 milliliters of that adjusted suspension (not the 1:10 dilution) to each liter of nutrient broth, prepared as directed in subdivision (ii) (*b*) of this subparagraph, needed for the test.

(*b*) *Working standard and standard solutions.* Prepare the standard stock solution as directed in subdivision (iii) of this subparagraph. Make dilutions of the stock solution with dimethylformamide to obtain concentrations of 121, 139, 160, 184, and 212 units per milliliter. These solutions are then diluted 1:10 with sterile distilled water to obtain concentrations of 12.1, 13.9, 16.0, 18.4, and 21.2 units per milliliter. Add 1.0 milliliter of each such concentration to each of six sterile 20 millimeters x 150 millimeters test tubes. Maintain the sterility of the tubes.

(*c*) *Preparation of sample.* Dissolve the sample to be tested in sufficient dimethylformamide to give a stock solution of convenient concentration. Dilute the stock solution with dimethylformamide to obtain a concentration of 160 units per milliliter (estimated). Further dilute this solution 1:10 with sterile distilled water to obtain a concentration of 16 units per milliliter (estimated). Add 1.0 milliliter of this dilution to each of six sterile 20 millimeters x 150 millimeters test tubes.

(*d*) *Procedure.* To each of the 20 millimeters x 150 millimeters test tubes prepared in (*b*) and (*c*) of this subdivision, add 9.0 milliliters of the inoculated nutrient broth described in (*a*) of this subdivision, and incubate at 26° C. for 16 hours to 18 hours. After incubation, add 0.5 milliliter of a 12 percent formaldehyde solution to each tube and read the absorbance values in a suitable photoelectric colorimeter, using a wavelength of 530 mμ. Set the instrument at zero absorbance with clear uninoculated broth prepared as described in subdivision (ii) (*b*) of this subparagraph.

(*e*) *Estimation of potency.* Plot the average values for each concentration of the standard on semilog graph paper

with absorbance values on the arithmetic scale and nystatin concentrations on the logarithmic scale. Construct the best straightline through the points, either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e}{5}$$

$$H=\frac{3e+2d+c-a}{5}$$

where

L = absorbance value for the lowest concentration of the standard curve.

H = absorbance value for the highest concentration of the standard curve.

a, b, c, d, e = average absorbance values for each concentration of the standard curve.

Plot the values obtained for L and H and connect the points with a straightline. Average the absorbance values for the sample and read the nystatin concentration from the standard curve. Multiply the concentration by appropriate dilution factors to obtain the nystatin content of the sample. Its content of nystatin is satisfactory if it is not less than 85 percent of the number of units that it is represented to contain.

(2) *Toxicity.* Inject intraperitoneally each of 5 mice, within the weight range of 18 grams to 25 grams, with 0.5 milliliter of a suspension of the drug containing 1,200 units per milliliter in a 0.5 percent acacia solution. If no animal dies within 48 hours, the sample is nontoxic. If one or more of the animals die within 48 hours, repeat the test with 5 unused mice weighing 20 grams (±0.5 gram) each; if all animals survive the repeat test, the sample is nontoxic.

(3) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(4) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a 3-percent aqueous suspension of the drug.

(5) *Identity.* Weigh approximately 20 milligrams of the sample in a 100-milliliter glass-stoppered volumetric flask, add about 75 milliliters absolute methyl alcohol, and shake mechanically for 30 minutes. Dilute to volume with methyl alcohol. Transfer 10.0 milliliters of this solution to a 100-milliliter volumetric flask and dilute to volume with methyl alcohol. Within 2 hours, determine the absorption peak at 230 mμ, 291 mμ, 305 mμ, and 319 mμ and the shoulder at 279±2 mμ, using a suitable ultraviolet spectrophotometer and quartz cells. Set the instrument to 100 percent transmission with absolute methyl alcohol. If a recording spectrophotometer is used, record the ultraviolet absorption spectrum from 220 mμ to 320 mμ. If a nonrecording spectrophotometer is used, the exact positions of the peaks and shoulder should be determined for the particular instrument used. The ratio of the two absorbancies (A_{max}/A_{min}) should be not less than 0.90 and not more than 1.25.

§ 141c.225 Tetracycline hydrochloride-nystatin tablets.

(a) *Tablets*—(1) *Potency*—(i) *Tetracycline hydrochloride content.* Proceed as directed in § 141c.224(a)(1)(i). Its content of tetracycline hydrochloride is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(ii) *Nystatin content.* Proceed as directed in § 141c.224 (a) (1) (ii). Its content of nystatin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5 (a) or § 141a.26 (e) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

(b) *Nystatin used in making the tablets.* Proceed as directed in § 141c.224 (b).

§ 141c.226 Tetracycline and vasoconstrictor suspension.

(a) *Potency.* Proceed as directed in § 141c.218(a). Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *pH.* Using the undiluted sample, proceed as directed in § 141a.5 (b) of this chapter.

§ 141c.227 Chlortetracycline spray dressing (chlortetracycline hydrochloride spray dressing).

(a) *Potency.* Spray the entire contents of the well shaken sample into a large tared beaker. Place in a vacuum desiccator, evacuate, and allow to stand at room temperature for 16 to 18 hours. After the gas has volatilized, accurately weigh the beaker and contents and determine the weight of the ointment ejected when used as directed in its labeling. Remove a representative quantity (usually 1 gram) of the ointment from the beaker, accurately determine its weight, and place in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Proceed as directed in § 141c.202(a). The content of the immediate container is satisfactory if it contains not less than 85 percent of the number of grams of ointment that it is represented to contain. The potency of the ointment is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline hydrochloride per gram that it is represented to contain.

(b) *Sterility.* Using an amount of spray (usually 5 to 8 seconds) equivalent to approximately 40 milligrams of chlortetracycline from each container tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Moisture.* Proceed as directed in § 141b.117(c) of this chapter, except dissolve the sample in 10 milliliters of dry chloroform.

§ 141c.228 Chlortetracycline hydrochloride-neomycin tablets veterinary; tetracycline hydrochloride-neomycin tablets veterinary.

(a) *Potency*—(1) *Chlortetracycline hydrochloride content.* Prepare the sample as follows: Using a mortar and pestle, grind 5 tablets to a fine powder. Using 200 milliliters of absolute methyl alcohol, quantitatively transfer the powder to a blending jar and blend at high speed for 2 minutes. Centrifuge a portion of the liquid at high speed for sufficient time (usually 15 minutes) to obtain a substantially clear solution. Dilute an aliquot of the clear solution in sufficient 0.10 *M* monobasic potassium phosphate buffer, pH 4.5, to give a concentration of 0.06 microgram per milliliter (estimated). Proceed as directed in § 141c.201(a)(8). Its content of chlortetracycline hydrochloride is satisfactory if it contains not less than 85 percent of the number of milligrams per tablet that it is represented to contain.

(2) *Tetracycline hydrochloride content.* Prepare the sample as directed in subparagraph (1) of this paragraph, except dilute the sample to an estimated concentration of 0.24 microgram per milliliter and proceed as directed in § 141c.218(a)(3). Its content of tetracycline hydrochloride is satisfactory if it contains not less than 85 percent of the number of milligrams per tablet that it is represented to contain.

(3) *Neomycin content.* Proceed as directed in § 141e.410(a)(1)(ii) of this chapter if Staphylococcus epidermidis is used as the test organism. If Staphylococcus aureus is used as the test organism proceed as follows:

Immediately after the second blending, heat a convenient size aliquot of the blend in a steam bath for 30 minutes, cool, and dilute to 10 micrograms per milliliter (estimated). Its content of neomycin is satisfactory if it contains 85 percent of the number of milligrams of activity per tablet that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141c.229 Tetracycline-nystatin oral suspension; tetracycline phosphate complex-nystatin oral suspension (tetracycline phosphate complex-nystatin oral drops).

(a) *Potency*—(1) *Tetracycline or tetracycline phosphate complex content.* Proceed as directed in § 141c.222(a). Its content of tetracycline or tetracycline phosphate complex is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Nystatin content.* Use 5 milliliters of the sample and proceed as directed in § 141c.224 (a) (1) (ii). Its content of nystatin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c) of this chapter.

§ 141c.230 Chlortetracycline hydrochloride powder topical; tetracycline hydrochloride powder topical.

(a) *Potency*—(1) *Dry powder.* Using a 3.0-gram sample or the entire contents of the immediate container for each determination, prepare the sample as follows: Using a high-speed blender, blend a 3.0-gram sample in a glass blending jar containing 500 milliliters of 0.01 *N* HCl (use 0.1 *N* HCl if it is tetracycline), or reconstitute in the immediate container as directed in the labeling of the drug.

Transfer an appropriate aliquot of 1.0 milliliter to 5.0 milliliters to a 100-milliliter volumetric flask and make to mark with 0.01 *N* HCl (use 0.1 *N* HCl if it is tetracycline). Withdraw an aliquot from the volumetric flask, and if it is chlortetracycline hydrochloride dilute to 0.06 μg per milliliter, using 0.1 *M* potassium phosphate buffer, pH 4.5, and proceed as directed in § 141c.201 (a). If it is tetracycline hydrochloride, dilute to 0.24 μg. per milliliter, using 0.1 *M* potassium phosphate buffer, pH 4.5, and proceed as directed in § 141c.218 (a). The average potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride per gram or per immediate container that it is represented to contain.

(2) *Powder packaged with inert gases.* Spray, as directed in the labeling, the entire contents of each container to be tested into a separate 2-liter Erlenmeyer flask, held in a horizontal position. Add 500 milliliters of 0.1 *N* HCl and shake to dissolve the contents. Immediately remove aliquots of this solution and, using 0.1 *M* potassium phosphate buffer, pH 4.5, for further dilutions, proceed as directed in § 141c.201(a) if it is chlortetracycline hydrochloride powder or § 141c.218(a) if it is tetracycline hydrochloride powder. Calculate the average total amount of antibiotic expelled from the containers. The total potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter, except if it is packaged with inert gases proceed as directed in § 141b.117 (c) of this chapter.

§ 141c.231 Capsules tetracycline and oleandomycin phosphate; capsules tetracycline and triacetyloleandomycin; capsules tetracycline hydrochloride and oleandomycin phosphate; capsules tetracycline hydrochloride and triacetyloleandomycin.

(a) *Potency*—(1) *Tetracycline or tetracycline hydrochloride content by turbidimetric assay*—(i) *Test culture and media.* Maintain the test organism *Escherichia coli* (ATCC 10536) on the agar described in § 141a.1(b)(1) of this chapter. For use in the assay, prepare a suspension of the organism every 2 weeks, as follows: Transfer the organism to a fresh agar slant and incubate at 37° C. overnight. Wash the growth from the slant with the aid of 2 milliliters of sterile distilled water and sterile glass beads into a Roux bottle containing 300 milliliters of the maintenance medium. Incubate overnight at 37° C. and then harvest the growth with 50 milliliters of sterile distilled water and sterile glass beads. Standardize this suspension by determining the dilution that will permit 40-percent light transmission in a photoelectric colorimeter using a 650-millimicron filter and an 18-millimeter diameter test tube as an absorption cell. Prepare the daily inoculum by adding 10 milliliters of that dilution to each liter of nutrient broth, prepared as directed in § 141a.1(b)(3) of this chapter, needed for the test.

(ii) *Working standard and solutions.* Dissolve an appropriate amount of the working standard in sufficient 0.1 *N* HCl to give a concentration of 1,000 micrograms per milliliter. This stock solution may be kept in the refrigerator for 1 week. Make daily dilutions of the stock solution with 0.1 *M* potassium phosphate buffer (pH 4.5) to obtain concentrations of 0.146, 0.187, 0.240, 0.308, and 0.395 micrograms per milliliter. Add 1.0 milliliter of each such concentration to each of three 16 millimeters x 125 millimeters test tubes.

(iii) *Preparation of sample.* Dissolve the contents of a representative number of capsules in sufficient 0.1 *N* HCl to give a stock solution of convenient concentration. Further dilute the stock solution with 0.1 *M* potassium phosphate buffer (pH 4.5) to obtain a final concentration of 0.24 microgram per milliliter (estimated). Add 1.0 milliliter of this dilution to each of three 16 millimeters x 125 millimeters test tubes.

(iv) *Procedure.* To each of the 16 millimeters x 125 millimeters test tubes prepared in subdivisions (ii) and (iii) of this subparagraph, add 9.0 milliliters of the inoculated nutrient broth described in subdivision (i) of this subparagraph and place immediately in a 37° C. water bath for 3 to 4 hours. After incubation, add 0.5 milliliter of a 12-percent formaldehyde solution to each tube and read the absorbance values in a suitable photoelectric colorimeter, using a wavelength of 530 millimicrons. Set the instrument at zero absorbance with clear uninoculated broth prepared as described in § 141a.1 (b) (3) of this chapter.

(v) *Estimation of potency.* Plot the average values for each concentration of the standard on arithmetic graph paper with absorbance values on the ordinate and tetracycline or tetracycline hydrochloride concentrations on the abscissa. Construct the best straightline through the points, either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e}{5},$$

$$H=\frac{3e+2d+c-a}{5},$$

where

L = absorbance value for the lowest concentration of the standard curve,

H = absorbance value for the highest concentration of the standard curve,

a, b, c, d, e = average absorbance values for each concentration of the standard curve.

Plot the values obtained for L and H and connect the points with a straight line. Average the absorbance values for the sample and read the tetracycline or tetracycline hydrochloride concentration from the standard curve. Multiply the concentration by appropriate dilution factors to obtain the tetracycline or tetracycline hydrochloride content of the sample. Its potency is satisfactory if it contains the equivalent of not less than 85 percent of the number of milligrams of tetracycline hydrochloride that it is represented to contain.

(2) *Oleandomycin content.* (i) If oleandomycin phosphate is used, proceed as directed in paragraph (c) (1) of this section, except prepare the sample as follows: Dissolve the contents of a representative number of capsules in sufficient 0.1 *M* potassium phosphate buffer (pH 8.0) to give a stock solution of convenient concentration. Further dilute with 0.1 *M* potassium phosphate buffer (pH 8.0) to obtain a final concentration of 5.0 μg. of oleandomycin activity per milliliter (estimated).

(ii) If triacetyloleandomycin is used, proceed as follows: Dissolve the contents of a representative number of capsules in chloroform to give a stock solution of 1.0 milligram of oleandomycin activity per milliliter. Transfer 30 milliliters of the chloroform solution to a glass-stoppered test tube (200 millimeters x 22 millimeters) and add 20 milliliters of 1 *N* sodium hydroxide. Shake for 1 minute and centrifuge briefly to aid in the separation of the layers. With the aid of a syringe and needle, remove and discard the aqueous layer. Repeat the washing procedure with two more 20-milliliter portions of 1 *N* sodium hydroxide solution. Filter the chloroform layer through a pledget of cotton. Dilute an aliquot of this solution with chloroform to give a solution containing approximately 25 μg. of oleandomycin per milliliter. Transfer a 5.0 milliliter aliquot to a 40 milliliter glass-stoppered centrifuge tube, dilute to 20 milliliters with chloroform, and determine the oleandomycin content as directed in paragraph (d) (1) (i) of this section.

Its content of oleandomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Oleandomycin phosphate used in making the capsules*—(1) *Potency*—(i) *Cylinders (cups).* Use cylinders described in § 141a.1 (a) of this chapter.

(ii) *Culture media.* (*a*) Use the nutrient agar described in § 141a.1(b)(1) of this chapter for the seed layer and base layer, except that its pH after sterilization is 7.8 to 8.0.

(*b*) Use the nutrient agar described in § 141a.1(b)(1) of this chapter for maintaining the test organism.

(iii) *Working standard.* Dissolve a suitable weighed quantity (usually 25 milligrams or less) of the working standard (obtained from the Food and Drug Administration) in 2 milliliters of ethanol, then add sufficient 0.1 *M* potassium phosphate buffer, pH 8.0, to give a concentration of 1,000 micrograms of oleandomycin base per milliliter. This stock solution may be kept in the refrigerator for 3 days.

(iv) *Preparation of sample.* Dissolve the sample in sufficient 0.1 *M* potassium phosphate buffer (pH 8.0) to give a convenient stock solution. Further dilute in 0.1 *M* potassium phosphate buffer (pH 8.0) to give a final concentration of 5.0 micrograms per milliliter (estimated).

(v) *Preparation of test organism.* The test organism is Staphylococcus epider-

midis (ATCC 12228), which is maintained on slants of agar described under subdivision (ii) (*a*) of this subparagraph. Wash the organism from the agar slant with 3 milliliters of sterile physiological saline solution onto a large agar surface such as that provided by a Roux bottle containing 300 milliliters of the agar described in subdivision (ii) (*a*) of this subparagraph. Spread the suspension of organisms over the entire agar surface with the aid of sterile glass beads. Incubate for 24 hours at 32° C. and then wash the resulting growth from the agar surface with about 30 milliliters of sterile physiological saline solution. Standardize the suspension by determining the dilution that will give 80-percent light transmission, using a suitable photoelectric colorimeter with a 650-millimicron filter and an 18-millimeter-diameter test tube as an absorption cell. Run test plates to determine the quantity of the diluted suspension (usually 1.5 milliliters) that should be added to each 100 milliliters of agar to give clear, sharp zones of inhibition of appropriate size.

(vi) *Preparation of plates.* Add 21 milliliters of the agar prepared as described in subdivision (ii) (*a*) of this subparagraph to each Petri dish (20 millimeters x 100 millimeters). Distribute the agar evenly in the plates and allow it to harden. Use the plates the same day they are prepared. Melt a sufficient amount of the agar described in subdivision (ii) (*a*) of this subparagraph, cool to 48° C., add the proper amount of the test organism as described in subdivision (v) of this subparagraph, and mix thoroughly. Add 4 milliliters of this inoculated agar to each Petri dish. Distribute the agar evenly in the plates, cover with porcelain covers glazed on the outside, and allow to harden. After the agar has hardened, place 6 cylinders on the agar surface so that they are at approximately 60° intervals on a 2.8-centimeter radius.

(vii) *Standard curve.* Prepare the daily standard curve by further diluting the 1,000 micrograms per milliliter stock solution in 0.1 *M* potassium phosphate buffer (pH 8.0) to obtain concentrations of 3.2, 4.0, 5.0, 6.25 and 7.80 micrograms per milliliter. Use 3 plates for the determination of each point on the curve, except the 5.0 micrograms per milliliter concentration, a total of 12 plates. On each of 3 plates fill 3 cylinders with the 5.0 micrograms per milliliter standard, and the other 3 cylinders with the concentration under test. Thus, there will be 36 five-microgram determinations and 9 determinations for each of the other points on the curve. After incubation, read the diameters of the circles of inhibition in the plates. Average the readings of the 5.0 micrograms per milliliter concentration and the readings of the point tested for each set of 3 plates and average also all 36 readings of the 5.0 micrograms per milliliter concentration. The average of the 36 readings of the 5.0 micrograms per milliliter concentration is the correction point for the curve. Correct the average value obtained for each point to the figure it would be if the 5.0 micrograms per milliliter reading for that set of 3 plates were the same as the correction point. Thus, if in correcting the 4.0-microgram concentration, the average of the 36 readings of the 5.0-microgram concentration were 20.0 millimeters, and the average of the 5.0-microgram concentration of this set of 3 plates were 19.8 millimeters, the correction would be +0.2 millimeter. If the average reading of the 4.0-microgram concentration of these same 3 plates were 19.0 millimeters, the corrected value would be 19.2 millimeters. Plot these corrected values, including the average of the 5.0 micrograms per milliliter concentration, on 2-cycle semilog paper, using the concentration in micrograms per milliliter as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Draw the standard curve through these points, either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e}{5},$$

$$H=\frac{3e+2d+c-a}{5},$$

where:

L=corrected zone diameter for the lowest concentration of the standard curve,

H=corrected zone diameter for the highest concentration of the standard curve,

c=average zone diameter of 36 readings of the 5.0 micrograms per milliliter standard,

a, b, d e=corrected average values for the 3.2, 4.0, 6.25, and 7.81 micrograms per milliliter standard solutions, respectively.

Plot the values obtained for L and H and connect with a straight line.

(viii) *Assay.* Use 3 plates for each sample. Fill 3 cylinders on each plate with the standard 5.0 micrograms per milliliter solution and 3 cylinders with the 5.0 micrograms per milliliter (estimated) sample, alternating standard and sample. Incubate all plates, including those containing the standard curve, at 32° C.–35° C. overnight, and measure the diameter of each circle of inhibition. To estimate the potency of the sample, average the zone readings of the standard and the zone readings of the sample on the 3 plates used. If the sample gives a larger zone size than the average of the standard, add the difference between them to the 5.0 micrograms per milliliter zone on the standard curve. If the average sample value is lower than the standard value, subtract the difference between them from the 5.0 micrograms per milliliter value on the curve. From the standard curve, read the potencies corresponding to these corrected values of zone sizes.

(2) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, except use physiological salt solution as the diluent, and inject 0.5 milliliter of a solution containing 8 milligrams per milliliter.

(3) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(4) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a solution containing 100 milligrams per milliliter.

(5) *Crystallinity.* Proceed as directed in § 141a.5 (c) of this chapter.

(d) *Triacetyloleandomycin used in making the capsules*—(1) *Potency*—(i) *Chemical method*—(*a*) *Reagents and equipment.* (*1*) Methyl orange reagent: Shake 0.5 *M* boric acid solution for about 12 hours (to insure saturation) with an excess of methyl orange indicator. An alternative method is to heat the mixture to about 50° C. and shake for about an hour. Then allow to cool. Filter the saturated dye solution and wash three times with chloroform. Store the dye solution over chloroform.

(*2*) Acid-alcohol solution: Add 2 milliliters of concentrated sulfuric acid to 98 milliliters of absolute methyl alcohol.

(*3*) Glycerin: Reagent grade.

(*4*) Centrifuge tubes: 40 milliliters, glass-stoppered.

(*b*) *Procedure.* Prepare a chloroform solution containing 50.0 milligrams activity of standard oleandomycin base in 200 milliliters of solution. Transfer 10.0 milliliters of the solution to a 100-milliliter volumetric flask and dilute to volume with chloroform. Transfer 2.0, 4.0, 6.0, and 8.0 milliliters of this solution to glass-stoppered centrifuge tubes (40-milliliter size) and dilute to a total volume of 20.0 milliliters each with chloroform. To the 20.0 milliliters of the solution present in each (40-milliliter size) centrifuge tube add 0.2 milliliter of glacial acetic acid, 0.20 milliliter of glycerin, and 0.40 milliliter of methyl orange reagent. Shake for 5 minutes and centrifuge for 3 minutes. Immediately transfer to another tube a 10.0-milliliter aliquot from the chloroform (lower) layer. Care must be exercised to see that no portion of the dye-glycerin-phase is included with the chloroform aliquot. Add 1.0 milliliter of acid-alcohol solution to this chloroform aliquot, mix well, and read the absorbancy at 535 mμ, using a 1-centimeter cell and a suitable photometer and using chloroform, similarly treated, as a blank. Prepare a standard curve, plotting the absorbance values of the standard solutions against the concentration expressed in micrograms per aliquot. Accurately weigh the sample to be tested to give 50 milligrams (estimated) of oleandomycin activity, dissolve in chloroform, and make to 200 milliliters with chloroform. Transfer 10.0 milliliters to a 100-milliliter volumetric flask and make to volume with chloroform. Transfer 5.0 milliliters to a glass-stoppered centrifuge tube and proceed as above. Determine the potency of the sample from the standard curve.

(ii) *Microbiological assay.* Proceed as directed in paragraph (c) (1) of this section, except use the triacetyloleandomycin standard as the standard of comparison. Dissolve the working standard in sufficient 80 percent isopropyl alcohol-water solution to give a concentration of 1,000 micrograms per milliliter (estimated). Prepare the standard curve by further diluting the stock solution in 0.1 *M* potassium phosphate buffer, pH 8.0, to give concentrations of 9.6, 12.0, 15.0, 18.7, and 23.4 micrograms per milliliter. The 15.0 micrograms per milliliter is the reference concentration. Prepare samples in the same manner as described for the stock solution and further dilute

in 0.1 *M* potassium phosphate buffer, pH 8.0, to a final concentration of 15.0 micrograms per milliliter (estimated).

(2) *Toxicity.* Administer orally, by means of a cannula or other suitable device, to each of five mice within the weight range of 18 grams to 25 grams, 0.5 milliliter of a suspension containing 200 milligrams per milliliter in normal saline solution. If no animal dies within 48 hours, the sample is nontoxic. If one or more animals die within 48 hours, repeat the test with five unused mice weighing 20 grams (±0.5 gram) each; if all animals survive the repeat test the sample is nontoxic.

(3) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(4) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a saturated aqueous-ethanol (1:1) solution prepared by adding 100 milligrams per milliliter.

(5) *Paper chromatograph method*—(i) *Apparatus and reagents*—(*a*) Chromatographic chamber (cylinder glass-stoppered museum jar 11.5 inches x 3.5 inches).

(*b*) Chromatographic paper (8 inches x 8 inches Whatman No. 1).

(*c*) 0.1 *N* hydrochloric acid.

(*d*) Resolving solvent: Butyl acetate, benzene, nitromethane, pyridine (5:5:5:1 by volume).

(*e*) Spray reagent: 15 grams antimony trichloride per 100 milliliters of chloroform.

(ii) *Procedure.* Dissolve the sample in chloroform to give a solution containing 10 milligrams to 20 milligrams per milliliter. Prepare a sheet of chromatographic paper by drawing a line of origin parallel to and 1 inch from the edge of the paper. Wet the paper thoroughly with the 0.1 *N* hydrochloric acid and blot it firmly between sheets of absorbent paper. Starting 2 inches in from the edge and at 1-inch intervals, apply 3 microliters to 5 microliters of the sample solutions to the starting line. Allow a few minutes for the paper to dry partially. While the paper is still damp, form a cylinder by bringing the outer edges together, allowing about 1-inch overlap, and secure with a paper clip. Stand the paper in the chromatographic chamber, which has been filled to a depth of ½-inch with the resolving solvent. After the solvent front rises to a height of 4 inches to 5 inches above the origin, remove the paper from the tank and hang it up to air dry. Spray the dried paper with the antimony trichloride reagent. Hang the paper in a 100° C. oven for 3 minutes. A purple spot becomes visible for triacetyloleandomycin at an R_f value of about 0.85. The approximate R_f values for diacetyloleandomycin, monoacetyloleandomycin, and oleandomycin are, respectively, 0.72, 0.27, and 0.13.

(6) *Acetyl determination*—(i) *Apparatus and reagents.* (*a*) One three-necked pyrex flask of approximately 45 milliliters capacity, pearshaped with T-joints, agar inlet tube, glass-stoppered funnel, glass condenser, and bubble counter.

(*b*) 50-milliliter Pyrex Erlenmeyer flask.

(*c*) 10-milliliter burette, calibrated in 0.02 milliliter.

(*d*) Anhydrous methanol, reagent grade.

(*e*) 2 *N* sodium hydroxide solution.

(*f*) Sulfuric acid solution prepared by adding 100 milliliters of concentrated H_2SO_4 to 200 milliliters of water.

(*g*) 1 *N* barium chloride solution.

(*h*) Phenolphthalein solution (1 percent in ethanol).

(*i*) Water-pumped nitrogen.

(*j*) NaOH solution, 0.015 *N*.

(ii) *Procedure.* Weigh accurately (to 0.01 milligram) approximately 30 milligrams of the sample into the three-necked acetyl flask. Add 2.0 milliliters of methanol to dissolve the sample, then add slowly with gentle swirling, 1.0 milliliter of NaOH solution. Connect the gas inlet tube with bubble counter attached, and adjust nitrogen flow to about two bubbles a second. Put glass-stoppered funnel in centerneck of acetyl flask and put about 5 milliliters of H_2O in the funnel. Add a boiling chip to the solution and attach condenser in the refluxing position with water cooling. Adjust burner flame under acetyl flask to reflux solution gently. Reflux for 30 minutes. Cool assembly slightly then rinse down condenser (still in reflux position) with a few milliliters of H_2O. Reassemble condenser to the distillation position and add water through the funnel to make a total of approximately 5 milliliters of H_2O added to acetyl flask. Adjust burner flame so that about 5 milliliters of H_2O and methanol is distilled over in approximately 10 minutes. Discard this distillate. Cool acetyl flask slightly. Acidify solution in flask by adding 1 milliliter of the sulfuric acid solution through the funnel. Adjust burner flame and distill over approximately 20 milliliters of distillate into an Erlenmeyer flask in about 20 minutes, adding water through the funnel as necessary. It is important to keep the liquid volume in the acetyl flask around 2 milliliters to 3 milliliters in order to obtain a quantitative recovery of the acetic acid. Collect a second fraction of distillate, about 10 milliliters in volume. As the second fraction is distilling, process the first fraction. Heat the first fraction and boil gently about 20 seconds. Add a few drops of $BaCl_2$ solution to check if any sulfate was distilled over. If the sulfate is present, discard and repeat the whole determination. If the sulfate is absent, immediately titrate the solution with the 0.015 *N* NaOH solution to a faint pink endpoint, using one drop of phenolphthalein solution as the indicator. Repeat the above procedure with the second fraction. If the second fraction requires less than 0.10 milliliter of the 0.015 *N* NaOH solution and all the acetic acid has been distilled over, the determination is completed. If greater than this, collect a third fraction of approximately 10 milliliters and titrate this as before. Total volumes of NaOH used and calculate results as follows:

$$\frac{\text{Milliliters of NaOH} \times N \text{ NaOH} \times 0.043 \times 100}{\text{Weight sample in grams}} = \text{Percent acetyl.}$$

(7) *Crystallinity.* Proceed as directed in § 141a.5(c) of this chapter.

§ 141c.232 Tetracycline phosphate complex.

(a) *Moisture, potency, toxicity, pH, crystallinity, absorptivity.* Proceed as directed in § 141c.220 (a), (b), (c), (d), (e), and (f).

(b) *Identity.* Proceed as directed in subparagraphs (1), (2), and (3) of this paragraph.

(1) *Presence of phosphate.* Suspend 100 milligrams of the sample in 10 milliliters of distilled water and filter a small portion by gravity. Transfer 1 milliliter to a 100-milliliter glass-stoppered cylinder, add 10 milliliters of distilled water, 2 milliliters of ammonium molybdate test solution, 1 milliliter of stannous chloride test solution, and 10 milliliters of isobutyl alcohol-benzene mixture (1:1 ratio), all in the order named. Shake vigorously for 1 minute, allow the layers to separate, and examine the top organic layer. In the presence of phosphate, the top layer turns blue.

(2) *Absence of chloride.* This test is used for detecting mixtures of tetracycline hydrochloride and phosphate salts. To 1 milliliter of the filtrate prepared as directed in subparagraph (1) of this paragraph, add 1 drop of silver nitrate test solution and 1 drop of nitric acid. Not more than a slight opalescence remains of the original precipitate in the absence of chloride.

(3) *Determination of percent tetracycline base.* This test is used to determine the quantity of tetracycline present as base in mixtures with phosphate salts.

(i) *Reagents.* (*a*) 1,4-Dioxane.

(*b*) Purified dioxane: Pass the dioxane through a column of Amberlite IRA 400 (OH^-) resin.

(*c*) Perchloric acid, 0.01*N*: Dilute 0.84 milliliter of 70 percent perchloric acid to 1,000 milliliters with purified dioxane; standardize at least once every 2 days, as follows: Weigh accurately about 70 milligrams of diphenylguanidine, and dissolve in 50 milliliters of ethyl alcohol in a 250-milliliter flask. Add two drops of methyl red, and titrate with the perchloric acid solution from a burette until the yellow color changes to orange. Deduct the volume of the perchloric acid consumed by 50 milliliters of the ethyl alcohol, and calculate the normality. Each 2.113 milligrams of diphenylguanidine is equivalent to 1 milliliter of 0.01*N* perchloric acid.

(*d*) Methyl red indicator: Dissolve 100 milligrams of methyl red in 100 milliliters of methyl alcohol.

(ii) *Procedure.* Place an accurately weighed 1-gram sample in a 50-milliliter Erlenmeyer flask, add 10.0 milliliters of purified dioxane and shake the mixture manually for about 2 minutes. Allow to settle, decant all the supernatant liquid into a 50-milliliter polyethylene centrifuge tube, cover with Parafilm, and centrifuge until clear (about 3 min-

utes). Pipette 5.0 milliliters of the clear, supernatant solution into a 50-milliliter beaker, stir magnetically, and titrate with 0.01*N* perchloric acid, using methyl red as the indicator. The endpoint is the last color change to orange when a drop of titrant is added.

Calculation:

$$\text{Percent tetracycline base} = \frac{\text{Milliliters of acid used} \times \text{normality} \times 0.4445 \times 200}{\text{Weight of sample}}$$

The sample is satisfactory if the results from the tests described indicate that there is a presence of phosphate, an absence of chloride, and not more than 1 percent of tetracycline base present.

§ 141c.233 Tetracycline - oleandomycin phosphate for oral suspension.

(a) *Potency*—(1) *Tetracycline content.* Proceed as directed in § 141c.231 (a) (1), except prepare the sample as follows: Reconstitute the powder as directed in the labeling of the drug. Transfer an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and dilute to mark with 0.1*N* HCl. Further dilute an aliquot of this solution with sufficient 0.1*M* potassium phosphate buffer (pH 4.5) to give a concentration of 0.24 μg. per milliliter (estimated). The average potency is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(2) *Oleandomycin content.* Proceed as directed in § 141c.231 (c) (1), except prepare the sample as follows: Reconstitute the powder as directed in the labeling of the drug. Dilute an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) with sufficient 0.1*M* potassium phosphate buffer (pH 8.0) to give a concentration of 5.0 μg. per milliliter (estimated). The average potency is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.26 (e) of this chapter.

(c) *pH.* Using the suspension prepared as directed in the labeling, proceed as directed in § 141a.5 (b) of this chapter.

§ 141c.234 Capsules tetracycline hydrochloride and novobiocin; capsules tetracycline phosphate complex and novobiocin.

(a) *Potency*—(1) *Tetracycline hydrochloride content; tetracycline phosphate complex content.* Proceed as directed in § 141c.231(a)(1). Its potency is satisfactory if it contains the equivalent of not less than 85 percent of the number of milligrams of tetracycline hydrochloride that it is represented to contain.

(2) *Novobiocin content.* Proceed as directed in § 141a.21 (a) (2) of this chapter. Its content of novobiocin is satisfactory if it contains not less than 85 percent of the number of milligrams per capsule that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141c.235 Tetracycline hydrochloride-oleandomycin phosphate for aqueous injection.

(a) *Potency*—(1) *Tetracycline hydrochloride content.* Proceed as directed in § 141c.231(a)(1), except prepare the sample as follows: Reconstitute the drug as directed in the labeling. Transfer an appropriate aliquot (usually 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and dilute to mark with 0.1 *N* HCl. Further dilute an aliquot of this solution with sufficient 0.1 *M* potassium phosphate buffer (pH 4.5) to give a concentration of 0.24 microgram per milliliter (estimated). The average potency is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(2) *Oleandomycin content.* Proceed as directed in § 141c.231 (c) (1), except prepare the sample as follows: Reconstitute the drug as directed in its labeling. Dilute an appropriate aliquot (usually 1.0 milliliter to 5.0 milliliters) with sufficient 0.1 *M* potassium phosphate buffer (pH 8.0) to give a concentration of 5.0 micrograms per milliliter (estimated). The average potency is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Sterility.* Using 40 milligrams from each container tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using 0.5 milliliter of a solution containing 1.0 milligram of tetracycline hydrochloride and 0.5 milligram of oleandomycin phosphate.

(d) *Pyrogens.* Proceed as directed in § 141a.3 of this chapter, using as a test dose 1 milliliter per kilogram of a solution containing 0.5 milligram of tetracycline hydrochloride and 0.25 milligram of oleandomycin phosphate.

(e) *Histamine.* Proceed as directed in § 141b.105 of this chapter, using as a test dose 0.6 milliliter per kilogram of a solution containing 5.0 milligrams of tetracycline hydrochloride and 2.5 milligrams of oleandomycin.

(f) *Moisture.* Proceed as directed in § 141a.5 or § 141a.26 (e) of this chapter.

(g) *pH.* Using the suspension prepared as directed in the labeling, proceed as directed in § 141a.5(b) of this chapter.

§ 141c.236 Tetracycline-nystatin for oral suspension.

(a) *Potency*—(1) *Tetracycline content.* Reconstitute the powder as directed in the labeling of the drug. Transfer an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and make to mark with 0.1 *N* HCl. Withdraw an aliquot from the volumetric flask and dilute to a concentration of 0.24 microgram per milliliter (estimated) using *M*/10 phosphate buffer, pH 4.5, and proceed as directed in § 141c.218 (a). Its content of tetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Nystatin content.* Reconstitute the powder as directed in the labeling of the drug. Transfer an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) to a blending jar containing 150 milliliters of dimethyl formamide. Blend for 2 minutes in a high-speed blender and then dilute an aliquot with sufficient dimethyl formamide to give a concentration of 400 units per milliliter (estimated). Further dilute this solution with 10 percent phosphate buffer, pH 6.0, to give a concentration of 20 units per milliliter (estimated). Proceed as directed in § 141c.224 (b). Its content of nystatin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) or § 141a.26 (e) of this chapter.

(c) *pH.* Using the suspension prepared as directed in the labeling, proceed as directed in § 141a.5 (b) of this chapter.

§ 141c.237 Chlortetracycline-neomycin-streptomycin ointment; chlortetracycline-neomycin-dihydrostreptomycin ointment; tetracycline hydrochloride-neomycin-streptomycin ointment; tetracycline hydrochloride-neomycin-dihydrostreptomycin ointment.

(a) *Potency*—(1) *Chlortetracycline content.* Proceed as directed in § 141c.201(a)(8), except prepare the sample by one of the following methods: Place an accurately weighed sample of approximately 1 gram in an extraction funnel prepared by fusing a ground-glass joint to the top of a medium-porosity sintered-glass filter funnel (30-millimeter diameter). Wash with five 10-milliliter portions of warm isooctane and draw off the ointment base under vacuum. Discard the isooctane washings. Wash the residue in the funnel four times with 10-milliliter portions of 0.3 percent piperidine in acetone solution. Withdraw each washing under vacuum. Combine the four washings in a 100-milliliter volumetric flask and make to mark with 0.1 *M* potassium phosphate buffer, pH 4.5. The solution for assay may also be prepared by placing a representative portion of the sample (usually 1.0 gram, accurately weighed) in a glass blending jar containing 199 milliliters of 0.01 *N* HCl and 1 milliliter of polysorbate 80. Using a high-speed blender, blend the mixture for 2 to 3 minutes and make proper estimated dilutions using 0.1 *M* potassium phosphate buffer, pH 4.5. Its content of chlortetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(2) *Tetracycline hydrochloride content.* Prepare the sample as directed in subparagraph (1) of this paragraph and proceed as directed in § 141c.218. Its content of tetracycline hydrochloride is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(3) *Neomycin content.* The residue remaining in the funnel after the extraction described in subparagraph (1) of this paragraph contains the neomycin and streptomycin or dihydrostreptomycin. Wash this residue five times, using 10-milliliter aliquots of 0.1 *M* potassium phosphate buffer, pH 8.0, drawing each washing off under vacuum. Combine the washings in a 100-milliliter volumetric flask and make to mark with 0.1 *M* potassium phosphate buffer, pH 8.0. Using an aliquot of this aqueous solution, proceed as directed in § 141a.65(a)(4) of this chapter. If Staphylococcus epidermidis is used as the test organism, proceed as directed in § 141a.411(a)(2) of this chapter. The content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(4) *Streptomycin content.* Using an aliquot of the aqueous solution prepared as directed in subparagraph (3) of this paragraph, proceed as directed in § 141b.101 (a) through (i) of this chapter. The content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(5) *Dihydrostreptomycin content.* Using an aliquot of the aqueous solution prepared as directed in subparagraph (3) of this paragraph, and the dihydrostreptomycin working standard as the standard of comparison, proceed as directed in § 141b.101 (a) through (i) of this chapter. The content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram of ointment that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b), of this chapter.

§ 141c.238 Tablets tetracycline hydrochloride and novobiocin.

(a) *Potency*—(1) *Tetracycline hydrochloride content.* Proceed as directed in § 141c.231(a)(1). Its tetracycline hydrochloride content is satisfactory if it contains not less than 85 percent of the number of milligrams per tablet that it is represented to contain.

(2) *Novobiocin content.* Proceed as directed in § 141a.21 (a) (2) of this chapter, except that penicillinase is not added, and if it contains calcium novobiocin the sample is blended in ethanol in lieu of 0.1 *N* potassium phosphate buffer. Its content of novobiocin is satisfactory if it contains not less than 85 percent of the number of milligrams per tablet that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Calcium novobiocin used in making the tablets*—(1) *Potency.* Proceed as directed in § 141a.21 (c) of this chapter, except prepare the sample as follows: Dissolve the sample for assay in sufficient ethanol to give a concentration of 3 milligrams per milliliter (estimated). Further dilute in 1.0 percent potassium phosphate buffer, pH 6.0, to give a final concentration of 0.5 μg. per milliliter (estimated).

(2) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, except inject 0.5 milliliter of a suspension containing 2 milligrams per milliliter.

(3) *Moisture, pH, crystallinity.* Proceed as directed in § 141a.5 (a), (b), and (c) of this chapter.

(d) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141c.239 Tetracycline-novobiocin for oral suspension.

(a) *Potency*—(1) *Tetracycline content.* Reconstitute the powder as directed in the labeling of the drug. Transfer an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and make to mark with 0.1 *N* HCl. Withdraw an aliquot from the volumetric flask and dilute to a concentration of 0.24 μg. per milliliter (estimated), using 0.1 *M* potassium phosphate buffer (pH 4.5) and proceed as directed in § 141c.231(a)(1). Its content of tetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(2) *Novobiocin content.* Reconstitute the powder as directed in the labeling of the drug. Transfer an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and make to mark using 0.1 *M* potassium phosphate buffer, pH 8.0 (except if it contains calcium novobiocin, ethanol is used in lieu of the buffer solution). Remove an aliquot and dilute with 1.0 percent potassium phosphate buffer, pH 6.0, to give a concentration of 0.5 μg. per milliliter (estimated). Proceed as directed in § 141a.21 (a) (2) of this chapter, except that penicillinase is not added. Its content of novobiocin is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141c.240 Tetracycline-triacetyloleandomycin syrup (tetracycline-triacetyloleandomycin oral drops; tetracycline-triacetyloleandomycin homogenized mixture); potency.

(a) *Tetracycline content.* Proceed as directed in § 141c.231(a)(1), except prepare the sample as follows: Transfer an appropriate sample (usually from 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and dilute to mark with 0.1 *N* HCl. Further dilute an aliquot of this solution with sufficient 0.1 *M* potassium phosphate buffer (pH 4.5) to give a concentration of 0.24 μg. per milliliter (estimated). Its tetracycline content is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(b) *Triacetyloleandomycin content.* Proceed as directed in § 141c.231 (d) (1) (i), except prepare the sample as follows: Transfer an appropriate sample (usually from 1.0 milliliter to 5.0 milliliters) to a glass-stoppered test tube (200 millimeters x 22 millimeters). Add 30 milliliters of chloroform and 20 milliliters of 1.0 *N* sodium hydroxide. Shake for 1 minute and centrifuge briefly to aid in the separation of the layers. Using a syringe and needle, remove and discard the aqueous layer. Repeat the washing with two more 20-milliliter portions of the sodium hydroxide solution. Filter the chloroform layer through a cotton pledget. Dilute an aliquot of the chloroform solution with chloroform to give a concentration of 25 μg. of oleandomycin activity per milliliter (estimated). Transfer a 5.0-milliliter aliquot to a 40-milliliter glass-stoppered centrifuge tube. Dilute to 20 milliliters with chloroform. Its triacetyloleandomycin content is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(c) *pH.* Using the undiluted sample, proceed as directed in § 141a.5 (b) of this chapter.

§ 141c.241 Chlortetracycline seed.

(a) *Potency.* Accurately weigh approximately 10 grams of the sample and place in a blending jar containing 500 milliliters of 0.01 *N* HCl. Blend for 3 minutes. Using an aliquot of the liquid, make the proper estimated dilutions in 10 *M* monopotassium phosphate buffer, pH 4.5, shake well, and proceed as directed in § 141c.201 (a) (8). Its content of chlortetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141c.242 Tetracycline-neomycin complex powder topical; tetracycline hydrochloride-neomycin sulfate powder topical.

(a) *Potency.*—(1) *Tetracycline-neomycin complex powder*—(i) *Tetracycline content.* Proceed as directed in § 141c.230(a)(2), except use water in lieu of 0.1 *N* HCl for dissolving the sample. Its tetracycline content is satisfactory if it contains not less than 85 percent of the equivalent number of milligrams of tetracycline hydrochloride that it is represented to contain.

(ii) *Neomycin content.* Using 0.1 *M* potassium phosphate buffer, pH 8.0, dilute an appropriate aliquot of the aqueous solution, prepared as directed in subparagraph (1) of this paragraph, to a final concentration of 1 μg. per milliliter (estimated), and proceed as directed in § 141c.231 (c) (1), except that the neomycin standard stock solution described in § 141e.410 (b) (1) (iii) of this chapter, is used to prepare the standard curve, by further diluting with pH 8.0 buffer to final concentrations of 0.64, 0.80, 1.0, 1.25, and 1.56 μg. per milliliter. The 1.0 μg. per milliliter solution is the reference concentration. In lieu of the method described in this subparagraph, the neomycin content may also be determined as follows: Using the aqueous solution described, prepare the sample and proceed as directed in § 141e.410 (b) (1) of this chapter, except use Staphylococcus aureus (American Type Culture Collection 12715) as the test organism, which is grown and maintained on agar containing 100 μg. of tetracycline hydrochloride per milliliter of agar. Its neomycin content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Tetracycline hydrochloride-neomycin sulfate powder*—(i) *Tetracycline hydrochloride content.* Prepare the sample as directed in § 141c.230(a)(2). Use an appropriate aliquot and proceed as directed in § 141c.218(a). Its tetracycline hydrochloride content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(ii) *Neomycin content.* Use an appropriate aliquot of the solution prepared in subdivision (i) of this subparagraph and proceed as directed in subparagraph (1)(ii) of this paragraph. Its neomycin content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Sterility.* Thoroughly cleanse the valve of each container to be tested with a suitable disinfectant. Carefully spray approximately 40 milligrams into each tube and proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used.

(c) *Moisture.* Proceed as directed in § 141b.117 (c) of this chapter.

(d) *Tetracycline-neomycin complex used in making the drug*—(1) *Potency*—(i) *Tetracycline content.* Dissolve the sample to be tested in sufficient water to give a convenient stock solution. Using an appropriate aliquot, proceed as directed in § 141c.218 (a).

(ii) *Neomycin content.* Using an aliquot of the stock solution prepared as directed in subdivision (i) of this subparagraph, proceed as directed in paragraph (a) (2) of this section, except the last sentence of that subparagraph.

(2) *Toxicity.* Proceed as directed in § 141a.4 of this chapter using 0.5 milliliter of a solution prepared by diluting the sample with physiological sodium chloride solution to contain 200 μg. of neomycin per milliliter (estimated).

(3) *pH.* Using a 1-percent aqueous solution, proceed as directed in § 141a.5 (b) of this chapter.

§ 141c.243 Capsules tetracycline hydrochloride-triacetyloleandomycin-nystatin.

(a) *Potency*—(1) *Tetracycline hydrochloride content.* Proceed as directed in § 141c.231(a)(1). Its tetracycline hydrochloride content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Triacetyloleandomycin content.* Proceed as directed in § 141c.231 (a) (2) (ii). Its content of triacetyloleandomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(3) *Nystatin content.* Proceed as directed in § 141c.224 (a) (1) (ii). Its content of nystatin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141c.244 Tetracycline hydrochloride-neomycin spray ointment topical.

(a) *Potency*—(1) *Tetracycline hydrochloride content.* Spray the entire contents of the well-shaken sample into a large tared beaker. Place in a vacuum desiccator, evacuate, and allow to stand at room temperature for 16 to 18 hours. After the gas has volatilized, accurately weigh the beaker and contents and determine the weight of the ointment ejected when used as directed in its labeling. Place an accurately weighed sample of approximately 1 gram in an extraction funnel prepared by fusing a ground-glass joint to the top of a medium-porosity sintered-glass filter funnel (30-millimeter diameter). Wash with five 10-milliliter portions of warm iso-octane and draw off the ointment base under vacuum. Discard the iso-octane washings. Wash the residue in the funnel four times with 10-milliliter portions of 0.3 percent piperidine in acetone solution. Withdraw each washing under vacuum. Combine the four washings in a 100-milliliter volumetric flask and make to mark with acetone. Remove an aliquot of this solution and proceed as directed in § 141c.218 (a). The sample may also be assayed by using a 1-gram sample weighed as described above and proceeding as directed in § 141c.202 (a). The tetracycline hydrochloride content is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(2) *Neomycin content.* The residue remaining in the funnel after the extraction described in subparagraph (1) of this paragraph contains the neomycin. Wash this residue five times, using 10-milliliter aliquots of 0.1 *M* potassium phosphate buffer, pH 8.0, drawing each washing off under vacuum. Combine the washings in a 100-milliliter volumetric flask and make to mark with 0.1 *M* potassium phosphate buffer, pH 8.0. Using an aliquot of this aqueous solution, proceed as directed in § 141e.410 (b) of this chapter. The sample may also be assayed by using a 1-gram sample weighed as described in subparagraph (1) of this paragraph and proceeding as directed in § 141c.242 (a) (2), except first prepare the sample by blending in an appropriate volume of 0.1 *M* potassium phosphate buffer, pH 8.0, using a high-speed blender. The content of neomycin is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(b) *Sterility.* Wipe the valve with a suitable disinfectant before spraying. Using an amount of spray (usually evacuated in 5 to 8 seconds) equivalent to approximately 20 milligrams of tetracycline hydrochloride for each container tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Moisture.* Proceed as directed in § 141b.117(c) of this chapter, except dissolve the sample in 10 milliliters of dry chloroform.

§ 141c.245 Tetracycline-triacetyloleandomycin for oral suspension.

(a) *Potency, toxicity, pH.* Prepare the drug as directed in its labeling and proceed as directed in § 141c.240.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141c.246 Tetracycline hydrochloride-neomycin in oil suspension.

(a) *Potency*—(1) *Content of tetracycline hydrochloride.* Proceed as directed in § 141c.237(a)(2) or § 141c.202 (a). Its content of tetracycline hydrochloride is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(2) *Contents of neomycin.* Proceed as directed in § 141c.237(a)(3) or as directed in § 141c.242(a)(2), except first prepare the sample by blending a 1-milliliter aliquot in an appropriate volume of 0.1 *M* potassium phosphate buffer, pH 8.0, using a high-speed blender. Its content of neomycin is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141c.247 Chlortetracycline hydrochloride impregnated surgical silk.

(a) *Potency.* Use not less than five sutures. Remove the needles, and place sutures in a glass-stoppered Erlenmeyer flask containing 50 milliliters of 0.1 *N* hydrochloric acid and allow to stand overnight, with frequent agitation, at room temperature. Remove a suitable aliquot and further dilute in 0.1 *M* phosphate buffer, pH 4.5, to the reference concentration, and proceed as directed in § 141c.201(a)(8). The potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline hydrochloride per suture that it is represented to contain.

(b) *Sterility.* Using individual sutures, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Moisture.* Using 10 sutures, proceed as directed in § 141a.5 of this chapter.

§ 141c.248 Rolitetracycline.

(a) *Potency.* Dry the rolitetracycline working standard (obtained from the Food and Drug Administration) for 3 hours at 60° C. under 5 millimeters or less pressure. Weigh a sufficient amount and proceed as directed in § 141c.201(a)(8) of this chapter, except:

(1) Prepare the standard stock solution by dissolving an appropriate amount of the working standard in sufficient methanol to give a concentration of 1,000 μg. per milliliter. This stock solution may be kept in refrigerator for 5 days.

(2) Dissolve the sample to be tested in sufficient methanol to give an appropriate stock solution. Further dilute in *M*/10 monopotassium phosphate buffer, pH 4.5, to give an estimated concentration of 0.24 μg. per milliliter.

(b) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using a test dose of 0.5 milliliter of an aqueous solution containing 2 milligrams per milliliter.

(c) *Moisture.* Proceed as directed in § 141a.26(e) of this chapter.

(d) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(e) *Absorptivity.* Proceed as directed in § 141c.218(e), except calculate on the anhydrous basis.

(f) *Crystallinity.* Proceed as directed in § 141a.5(c) of this chapter.

(g) *Identity.* Place approximately 100 milligrams of the sample to be tested in a test tube, add 5 milliliters of 1 *N* NaOH and heat gently to boiling for about 15 seconds. (The musty, amine-like odor of pyrrolidine is detectable.) Allow to cool to room temperature. The clear solution has a deep Burgundy-red color.

§ 141c.249 Rolitetracycline for intravenous use.

(a) *Potency.* Reconstitute the sample as directed on the label. Using a suitable syringe, withdraw a one-dose aliquot and place in a flask. Add sufficient methanol to give a solution containing 1 milligram per milliliter (estimated), and proceed as directed in § 141c.248(a). Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141c.201(b).

(c) *Toxicity.* Proceed as directed in § 141c.248(b).

(d) *Pyrogens.* Proceed as directed in § 141c.218(c).

(e) *Histamine.* Proceed as directed in § 141b.105 of this chapter, using as a test dose 0.6 milliliter per kilogram of a solution containing 5 milligrams per milliliter prepared by using sodium chloride solution as the diluent.

(f) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(g) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

§ 141c.250 Rolitetracycline for intramuscular use.

(a) *Potency.* Proceed as directed in § 141c.249(a). Its potency is satisfactory if it contains not less than 90 percent of the number of milligrams that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141c.201(b).

(c) *Pyrogens.* Proceed as directed in § 141c.218(c).

(d) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(e) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(f) *Histamine in the rolitetracycline used in making the batch.* Proceed as directed in § 141b.105 of this chapter, using as a test dose 0.6 milliliter per kilogram of a solution containing 5 milligrams per milliliter prepared by using sodium chloride solution as the diluent.

§ 141c.251 Demethylchlortetracycline hydrochloride.

(a) *Potency—(1) Turbidimetric assay—(i) Test culture and media.* Proceed as directed in § 141c.201(a)(8)(i).

(ii) *Working standard and solutions.* Prepare a stock solution by dissolving an appropriate aliquot of the dried demethylchlortetracycline hydrochloride standard in sufficient 0.1 *N* HCl to give a concentration of 1000 μg. per milliliter. Keep in a glass-stoppered flask and store in a refrigerator for not more than 1 week. Prepare solutions for the daily standard curve by diluting an aliquot of the stock solution in 0.1 *M* phosphate buffer, pH 4.5, to the following concentrations: 0.060, 0.077, 0.100, 0.129, and 0.167 μg. per milliliter. Place 1 milliliter of each concentration in each of three replicate tubes (16 mm. x 125 mm. outside dimensions). To each tube add 9 milliliters of inoculated broth described in subdivision (i) of this subparagraph, and place immediately in a water bath at 37° C. for 3 to 4 hours. Remove the tubes and add 0.5 milliliter of a 12-percent solution of formalin to each tube.

(iii) *Preparation of sample.* Prepare an appropriate stock solution of the sample in 0.1 *N* HCl. Dilute further in pH 4.5 buffer to a final estimated concentration 0.10 μg. per milliliter. Add 1 milliliter of this final concentration to each of three replicate tubes and proceed as described for the standard solution tubes in subdivision (ii) of this subparagraph. After incubation and the addition of the formalin to all tubes (standard and sample), read the absorbance values in a suitable photoelectric colorimeter, using a wavelength of 530 mμ. Set the instrument at zero absorbance with uninoculated broth.

(iv) *Estimation of potency.* Plot the average values for each concentration of the standard on one-cycle semilogarithmic graph paper with absorbance values on the arithmetic scale and concentrations on the logarithmic scale. Construct the best straight line through the points either by inspection or by means of the equation described in § 141c.231(a)(1)(v). Average the absorbance values for the sample and read the value from the standard curve. Multiply the concentration by appropriate dilution factors to obtain the demethylchlortetracycline hydrochloride content of the sample.

(b) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of an aqueous solution containing 2 milligrams per milliliter.

(c) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

(d) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(e) *Absorptivity.* Proceed as directed in § 141c.220(f).

(f) *Crystallinity.* Proceed as directed in § 141a.5(c) of this chapter.

(g) *Identity.* Exactly weigh a 40-milligram sample and place in a 200-milliliter volumetric flask. Add 100 milliliters of 0.1 *N* HCl and place on a shaker until the sample is dissolved. Dilute to mark with 0.1 *N* HCl and mix well. Transfer a 5.0-milliliter aliquot of the sample to each of two 50-milliliter volumetric flasks. To one add 10.0 milliliters of 6 *N* HCl and to the other add 10.0 milliliters of 3 *N* HCl. Treat a standard in the same manner as the sample. Place the acid-treated flask in an autoclave and turn on steam. The pressure should never exceed 10 pounds. Start timing when the temperature of the exhaust starts to rise. After 5 minutes decrease the pressure so that it will be zero after a total time of 11 minutes. Remove the flasks and place in a cold water bath. When cool, dilute to mark with water and mix well. Using a suitable spectrophotometer, place the 6 *N* HCl treated sample into the reference cell and read against the 3 *N* HCl treated sample at 368 mμ. Reverse the order of the cells in the cell holder and read at 430 mμ.

$$\frac{(A368\ \text{sample}+A430\ \text{sample})\ (\text{standard in milligrams per milliliter})}{(A368\ \text{standard}+A430\ \text{standard})\ (\text{sample in milligrams per milliliter})}=0.9\ \text{to}\ 1.1.$$

§ 141c.252 Capsules demethylchlortetracycline hydrochloride.

(a) *Potency.* Using a high-speed blender, prepare an appropriate number of capsules in 500 milliliters of 0.1 *N* HCl and proceed as directed in § 141c.251(a). The average potency is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

§ 141c.253 Demethylchlortetracycline.

(a) *Potency.* Proceed as directed in § 141c.251(a).

(b) *Toxicity.* Proceed as directed in § 141c.220(c).

(c) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

(d) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(e) *Absorptivity.* Proceed as directed in § 141c.220(f).

(f) *Crystallinity.* Proceed as directed in § 141a.5(c) of this chapter.

(g) *Identity.* Using the demethylchlortetracycline hydrochloride as the standard, proceed as directed in § 141c.251(g). The calculation shows a range for demethylchlortetracycline between 0.97 and 1.17.

§ 141c.254 Demethylchlortetracycline for oral suspension.

(a) *Potency.* Reconstitute as directed in the labeling. Remove an appropriate aliquot and proceed as directed in § 141c.251(a). Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

§ 141c.255 Demethylchlortetracycline syrup (demethylchlortetracycline oral drops).

(a) *Potency.* Use an appropriate aliquot of the sample to be tested and proceed as directed in § 141c.251(a). Its potency is satisfactory if it contains not less than 85 percent of the equivalent number of milligrams of demethylchlortetracycline hydrochloride that it is represented to contain.

(b) *pH.* Using the undiluted sample, proceed as directed in § 141a.5(b) of this chapter.

§ 141c.256 Chlortetracycline hydrochloride in oil oral veterinary.

(a) *Potency.* Proceed as directed in § 141c.202(a). The potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chlortetracycline hydrochloride that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141c.257 Tetracycline-amphotericin B for oral syrup; tetracycline-amphotericin B for oral drops.

(a) *Potency*—(1) *Tetracycline content.* Proceed as directed in § 141c.236 (a)(1). Its content of tetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Amphotericin B content.* Reconstitute the powder as directed in the labeling of the drug. Transfer an appropriate aliquot to a volumetric flask and make to mark with dimethyl sulfoxide. Remove an aliquot and dilute with dimethyl sulfoxide to give a concentration of 20 micrograms per milliliter (estimated). Further dilute this solution with 0.2 *M* phosphate buffer, pH 10.5, to give a concentration of 1.0 μg. per milliliter. Proceed as directed in paragraph (c) of this section. Its content of amphotericin B is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

(c) *Amphotericin B used in making the powder*—(1) *Potency*—(i) *Plate assay.* Use the amphotericin B standard as the standard of comparison and proceed as directed in § 141c.224 (b)(1)(i) through (b)(1)(viii), except that:

(ii) *Working standard.* The amphotericin B standard is stored under a nitrogen seal in the presence of a desiccant at −15° C. to −20° C. Dry approximately 30 milligrams of the standard, using the method described in § 141a.5(a) of this chapter. Dissolve a weighed portion of the dried standard in sufficient dimethyl sulfoxide to give a stock solution containing 1,000 μg. per milliliter. This solution should be used for 1 day only.

(iii) *Buffer.* Use 0.2 *M* phosphate buffer, pH 10.5, with the following composition: Dipotassium phosphate, 35 grams; 10 *N* NaOH, 2 milliliters. Make to 1 liter using distilled water.

(iv) *Preparation of sample.* Dissolve the sample in sufficient dimethyl sulfoxide to give a convenient stock solution. Further dilute with dimethyl sulfoxide to a concentration of 20 μg. per milliliter (estimated). Remove an aliquot and dilute to a concentration of 1.0 μg. per milliliter (estimated) using 0.2 *M* phosphate buffer, pH 10.5.

(v) *Standard curve.* Dilute the working stock solution with dimethyl sulfoxide to give concentrations of 39.2, 28.0, 20.0, 14.2, and 10.0 μg. per milliliter, respectively. Dilute one volume of each of these solutions with 19 volumes of phosphate buffer, pH 10.5, to give final concentrations of 1.96, 1.4, 1.0, 0.71, and 0.5 micrograms per milliliter. The 1.0 microgram per milliliter solution is the reference concentration.

(2) *Turbidimetric assay.* Proceed as directed in § 141c.224(b)(1)(ix) with the following exceptions:

(i) *Culture media.* Use ingredients that conform to the standards, if any, prescribed by the U.S.P. or N.F.

(a) Make yeast-beef agar for carrying the organism as follows:

Peptone	6.0 grams.
Yeast extract	3.0 grams.
Beef extract	1.5 grams.
Dextrose	1.0 gram.
Agar	15.0 grams.
Distilled water to make	1,000 milliliters.
pH 6.6 after sterilization.	

(b) Make yeast-beef broth for preparing an inoculum of the test organism:

Beef extract	1.5 grams.
Yeast extract	6.5 grams.
Peptone	5.0 grams.
Tryptone	10.0 grams.
Glucose	11.0 grams.
Sodium chloride	3.5 grams.
Dipotassium phosphate	3.68 grams.
Monopotassium phosphate.	1.32 grams.
Distilled water to make	1,000 milliliters.
pH 6.6 after sterilization.	

(c) Make yeast-beef assay broth:

Beef extract	1.5 grams.
Yeast extract	1.5 grams.
Peptone	5.0 grams.
Glucose	11.0 grams.
Sodium chloride	3.5 grams.
Dipotassium phosphate	3.68 grams.
Monopotassium phosphate	1.32 grams.
Distilled water to make	1,000 milliliters.
pH 6.6 after sterilization.	

In lieu of preparing the media from the individual ingredients as specified, they may be prepared from a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such media. Minor modifications of the specified individual ingredients are permissible if the resulting media possess growth-promoting properties at least equal to the media described.

(d) *Working standard and standard solutions.* Use the working standard described in paragraph (c)(1)(ii) of this section. Dissolve in dimethyl sulfoxide to obtain a concentration of 2 milligrams per milliliter. Further dilute to obtain a concentration of 30 μg. per milliliter, using 25 percent dimethyl sulfoxide (1 part dimethyl sulfoxide plus 3 parts distilled water). Use 1 percent potassium phosphate buffer, pH 6.0, and dilute to a concentration of 1 μg. per milliliter. Further dilute this solution with distilled water and prepare the standard curve containing concentrations of 0, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, and 0.10 μg. per tube. Add 1.0 milliliter of each concentration in each of 6 sterile 20 millimeter x 150 millimeter test tubes.

(e) *Preparation of sample.* Prepare the sample to be tested, using the same procedure as described for the standard solutions, obtaining 6 tubes each containing 0.05 μg. per tube.

(f) *Preparation of test organism.* The test organism is *Candida tropicalis* (ATCC 13803), which is maintained on slants of agar described in subparagraph (2)(i)(a) of this paragraph. Prepare the daily inoculum by transferring the culture from a stock slant to 100 milliliters of the broth described in subparagraph (2)(i)(b) of this paragraph and incubate for 16 hours to 18 hours at 30° C., with constant shaking.

(g) Incubate all standard and sample tubes at 30° C. with constant shaking for 3 hours to 5 hours.

(3) *Toxicity.* Administer orally, by means of a cannula or other suitable device, to each of 5 mice, within the weight range of 18 to 25 grams, 0.4 milliliter of a suspension of the drug containing 50 milligrams per milliliter in 0.5 percent gum acacia solution. If no animal dies within 48 hours, the sample is nontoxic. If one or more animals die within 48 hours, repeat the test with 5 unused mice weighing 20 grams (±0.5 gram) each; if all animals survive the repeat test the sample is nontoxic.

(4) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(5) *pH.* Using a 3.0 percent aqueous suspension, proceed as directed in § 141a.5(b) of this chapter.

(6) *Identity.* Accurately weigh 50.0 milligrams of the sample into a dry 50-milliliter volumetric flask. Add exactly 5 milliliters of dimethyl sulfoxide and dissolve. Make to mark with methanol and mix thoroughly. Pipet 4 milliliters of this solution into a 50-milliliter volumetric flask. Add methanol to the mark and mix thoroughly. The sample has absorption peaks at identical wavelengths with that of the standard (272, 282, 295, 362, 381, and 405 mμ).

(7) *Amphotericin A content*—(i) *Amphotericin A.* On a semimicrobalance, weigh accurately about 5 milligrams of an amphotericin A reference standard into a dry 50-milliliter volumetric flask. Add exactly 5.0 milliliters

of dimethyl sulfoxide and dissolve. Make to mark with methanol and mix thoroughly. Pipet 4.0 milliliters of this solution into a 50-milliliter volumetric flask. Add methanol to mark and mix thoroughly.

(ii) *Amphotericin B.* Accurately weigh about 50.0 milligrams of an amphotericin B working standard into a dry 50-milliliter volumetric flask and proceed as directed in subdivision (i) of this subparagraph.

(iii) *Sample.* Use 50.0 milligrams of the sample to be tested, and proceed as directed in subdivision (i) of this subparagraph. The standards should be used for 1 day only.

(iv) *Blank.* Pipet 5.0 milliliters of dimethyl sulfoxide into a 50-milliliter volumetric flask. Make to mark with methanol and mix. Pipet 4.0 milliliters of this solution into a 50-milliliter volumetric flask. Make to mark with methanol and mix thoroughly.

(v) *Procedure.* Use a suitable quartz spectrophotometer and 1-centimeter silica cells. Adjust the instrument to zero with the blank solution. Measure the absorbancies of the solutions of standard A, standard B, and the sample at 304 mμ and at 282 mμ. Calculate the absorptivity of each standard at both wavelengths.

$$\text{Percent amphotericin A} = \frac{[(B \times S_2) - (b \times S_1)] \times 625}{\text{Weight of sample in grams} \times [(B \times a) - (b \times A)]}$$

where:

A = absorptivity (1%, 1 cm.) of amphotericin A standard at 282 mμ.
B = absorptivity (1%, 1 cm.) of amphotericin B standard at 282 mμ.
a = absorptivity (1%, 1 cm.) of amphotericin A standard at 304 mμ.
b = absorptivity (1%, 1 cm.) of amphotericin B standard at 304 mμ.
S_1 = absorbance of sample at 282 mμ.
S_2 = absorbance of sample at 304 mμ.

§ 141c.258 Demethylchlortetracycline hydrochloride ointment.

(a) *Potency.* Proceed as directed in § 141c.251(a), except prepare the sample as follows: Place a representative portion of the sample (usually 1.0 gram, accurately weighed) in a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake ointment and ether until homogeneous. Shake with a 25-milliliter portion of 0.1 *N* HCl. Remove the acid layer and repeat the extraction with three 25-milliliter quantities of 0.1 *N* HCl. Combine the extracts and make the proper estimated dilutions in 0.1 *M* monopotassium phosphate buffer, pH 4.5. The sample may also be prepared by placing a representative portion of the sample (usually 1.0 gram, accurately weighed) in a glass blending jar containing 200 milliliters of 0.1 *N* HCl. Using a high-speed blender, blend for 3 minutes and make proper estimated dilutions using 0.1 *M* monopotassium phosphate buffer, pH 4.5. Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141c.259 Demethylchlortetracycline hydrochloride-nystatin capsules.

(a) *Potency*—(1) *Demethylchlortetracycline hydrochloride content.* Using a high-speed blender, prepare an appropriate number of capsules in 500 milliliters of 0.1 *N* HCl and proceed as directed in § 141c.251(a). The average potency is satisfactory if it contains not less than 85 percent of the number of milligrams of demethylchlortetracycline hydrochloride that it is represented to contain.

(2) *Nystatin content.* Proceed as directed in § 141c.224(a)(1)(ii). Its content of nystatin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 141c.260 Capsules tetracycline phosphate complex-amphotericin B.

(a) *Potency*—(1) *Tetracycline phosphate complex content.* Proceed as directed in § 141c.204(a) for tetracycline phosphate complex capsules. Its potency is satisfactory if it contains the equivalent of not less than 85 percent of the number of milligrams of tetracycline hydrochloride that it is represented to contain.

(2) *Amphotericin B content.* Prepare the sample for assay by placing a representative number of capsules in a blending jar with sufficient dimethyl sulfoxide to give a stock solution of convenient concentration. Blend for 2 minutes in a high-speed blender, then dilute an aliquot with sufficient dimethyl sulfoxide to give a concentration of 20 micrograms per milliliter (estimated). Further dilute this solution with 0.2*M* phosphate buffer, pH 10.5, to give a concentration of 1.0 microgram per milliliter. Proceed as directed in § 141c.257(c). Its content of amphotericin B is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

§ 141c.261 Tetracycline-novobiocin oral suspension (tetracycline-novobiocin oral drops; tetracycline-novobiocin syrup).

(a) *Potency*—(1) *Tetracycline content.* Proceed as directed in § 141c.239(a)(1). Its tetracycline content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Novobiocin content.* Proceed as directed in § 141c.239(a)(2). Its novobiocin content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *pH.* Using the undiluted sample, proceed as directed in § 141a.5(b) of this chapter.

§ 141c.262 Tetracycline-amphotericin B syrup; tetracycline-amphotericin B oral drops.

(a) *Potency*—(1) *Tetracycline content.* Transfer an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and make to mark with 0.1 *N* HCl. Withdraw an aliquot from the volumetric flask and dilute to a concentration of 0.24 microgram per milliliter (estimated) using *M*/10 phosphate buffer, pH 4.5, and proceed as directed in § 141c.218(a). Its content of tetracycline is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Amphotericin B content.* Transfer an appropriate aliquot to a volumetric flask and make to mark with dimethyl sulfoxide. Remove an aliquot and dilute with dimethyl sulfoxide to give a concentration of 20 micrograms per milliliter (estimated). Further dilute this solution with 0.2 *M* phosphate buffer, pH 10.5, to give a concentration of 1.0 microgram per milliliter. Proceed as directed in § 141c.257(c). Its content of amphotericin B is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *pH.* Using the undiluted sample proceed as directed in § 141a.5(b) of this chapter.

§ 141c.263 Demethylchlortetracycline-nystatin for oral suspension.

(a) *Potency*—(1) *Demethylchlortetracycline content.* Reconsititute as directed in the labeling. Remove an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) and proceed as directed in § 141c.251(a). Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Nystatin content.* Reconstitute as directed in the labeling. Transfer an appropriate aliquot (usually from 1.0 milliliter to 5.0 milliliters) to a blending jar containing 150 milliliters of dimethylformamide. Blend for 2 minutes in a high-speed blender and then dilute an aliquot with sufficient dimethylformamide to give a concentration of 400 units per milliliter (estimated). Further dilute this solution with 10 percent phosphate buffer, pH 6.0, to give a concentration of 20 units per milliliter (estimated). Proceed as directed in § 141c.224(b). Its content of nystatin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) or § 141a.26(e) of this chapter.

§ 141c.264 Chlortetracycline bisulfate.

(a) *Potency.* Using a 3.0-gram sample, proceed as directed in § 141c.201(a), except § 141c.201(a)(9).

(b) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using as a test dose 0.4 milliliter of an aqueous solution containing 2 milligrams of chloretetracycline hydrochloride equivalent per milliliter.

(c) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(d) *Butyl alcohol content*—(1) *Ceric nitrate reagent.* Dissolve 20 grams of ceric ammonium nitrate ($(NH_4)_2Ce(NO_3)_6 \cdot 2H_2O$) in 4 *M* HNO_3 and make up to 100 milliliters with 4 *M* HNO_3.

(2) *Sample.* Accurately weigh an amount of sample calculated to contain approximately 30 milligrams of butyl alcohol and transfer it to a 50-milliliter round-bottom distillation flask. Dissolve the sample in 25 milliliters of distilled water, add a small amount of antifoam agent, and connect to a condenser terminating in an adapter. The end of the adapter is inserted deep into a 25-milliliter graduated cylinder, which stands in an ice water bath. Distill slowly until 7 to 8 milliliters have collected. Warm the distillate to room temperature, transfer to a 10-milliliter volumetric flask, using not more than 1 milliliter of water to rinse out the graduate, and make up to 10 milliliters. Pipette 5 milliliters of this into a test tube, add 2 milliliters of the ceric nitrate reagent, and mix.

(3) *Standard.* Prepare a standard made by diluting 3 milliliters of reagent grade *n*-butyl alcohol with about 800 milliliters of distilled water in a 1,000-milliliter volumetric flask, shaking until solution is complete, then diluting to the mark with water. Use 5 milliliters of this plus 2 milliliters of ceric nitrate reagent as the standard.

(4) *Blank solution.* Prepare a blank made by mixing 5 milliliters of distilled water with 2 milliliters of the ceric nitrate reagent.

(5) *Procedure.* Use a suitable spectrophotometer and 1-centimeter cells. Adjust the instrument to zero absorbance with the blank solution. Immediately read the absorbancies of the sample and the standard at 475 millimicrons. Calculate the percent butyl alcohol as follows:

$$\text{Percent butyl alcohol} = \frac{A \text{ sample} \times 0.003 \times 10 \times 0.81 \times 100}{A \text{ standard} \times 0.98 \times w},$$

Where:

A sample is the absorbance of the sample at 475 millimicrons;

A standard is the absorbance of the butyl alcohol standard containing 0.003 milliliter/milliliter;

w is the weight of sample in grams;

0.81 is the density of butyl alcohol; and

The factor 0.98 corrects for incomplete recovery of butyl alcohol in the distillation step.

(e) *Percent sulfate.* Transfer an accurately weighed sample of approximately 1.0 gram to a 250-milliliter beaker. Add about 100 milliliters of distilled water and stir to dissolve. Neutralize the solution to litmus paper with 1:1 ammonium hydroxide, and warm. If precipitation occurs, filter and wash the filter paper with warm water. Neutralize the filtrate to litmus with 1:1 HCL and add 4 milliliters excess. Bring the solution to a boil and add, with constant stirring, sufficient boiling 10 percent barium chloride solution to precipitate all the sulfate, and a slight excess. Digest on a steam bath for 1 hour. Filter through Whatman No. 40 filter paper or equivalent. Wash the precipitate with hot water until the washings give no test for chloride with 0.1*N* silver nitrate solution. Transfer the filter paper and precipitate to a tared porcelain crucible. Dry over a low flame; then carefully burn off the filter paper. Finally, heat strongly but do not blast. Cool the crucible and weigh. After substracting the weight of the crucible, the residue is barium sulfate. By use of the following formula, calculate the percent sulfate in sample.

$$\frac{\text{Weight } BaSO_4 \times 0.4115 \times 100}{\text{Weight of sample}} = \text{percent sulfate.}$$

(f) *Absorptivity.* Accurately weigh approximately 100 miligrams of the sample and place in a 100-milliliter volumetric flask. Dissolve the sample in approximately 40 milliliters of distilled water by mixing thoroughly. Dilute to exactly 100 milliliters with distilled water and mix thoroughly. Transfer a 10.0 milliliter aliquot of this solution to a 250-milliliter volumetric flask, dilute to mark with 0.1 *N* hydrochloric acid, and mix thoroughly. Determine the absorbance of the solution at 368 millimicrons compared with distilled water as a blank. Use a suitable spectrophotometer for the absorbance measurements.

$$\text{Absorptivity (1\%, 1 cm.)} = \frac{\text{Absorbance at 368 m}\mu \times 2{,}500 \times 10}{\text{Weight of sample in milligrams} \times (100 - M - B)},$$

Where:

M = percent moisture in the sample;

B = percent butyl alcohol in the sample.

(g) *Crystallinity.* Proceed as directed in § 141a.5(c) of this chapter.

§ 141c.265 Chlortetracycline bisulfate soluble powder veterinary.

(a) *Potency.* Using an accurately weighed sample of approximately 500 milligrams, proceed as directed in § 141c.201(a) of this part, except § 141c.201(a)(9). Its potency is satisfactory if it contains not less than 85 percent and not more than 125 percent of the labeled potency.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

PART 141d—CHLORAMPHENICOL AND CHLORAMPHENICOL-CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

Sec.

141d.301 Chloramphenicol.
141d.302 Chloramphenicol capsules; potency.
141d.303 Chloramphenicol ointment; potency.
141d.304 Chloramphenicol ophthalmic.
141d.305 Chloramphenicol palmitate.
141d.306 Chloramphenicol palmitate oral suspension.
141d.307 Chloramphenicol solution; chloramphenicol for aqueous injection.
141d.308 Chloramphenicol otic; chloramphenicol topical.
141d.309 Chloramphenicol-streptomycin capsules; chloramphenicol-dihydrostreptomycin capsules.
141d.310 Chloramphenicol tablets.
141d.311 Chloramphenicol palmitate-streptomycin oral suspension; chloramphenicol palmitate-dihydrostreptomycin oral suspension.
141d.312 Chloramphenicol-neomycin ointment.
141d.313 Chloramphenicol-polymyxin ointment; potency.
141d.314 Chloramphenicol sodium succinate.
141d.315 Chloramphenicol sodium succinate for acqueous injection.
141d.316 Chloramphenicol - paromomycin ointment.

AUTHORITY: §§ 141d.301 to 141d.316 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 141d.301 Chloramphenicol.

(a) *Potency*—(1) *Cylinders (cups).* Use cylinders described under § 141a.1 (a) of this chapter.

(2) *Culture media.* Use the medium described under § 141a.1 (b) (1) of this chapter for both the seed layer and the base layer. Use the nutrient broth described under § 141a.1 (b) (3) of this chapter for preparing a suspension of the test organism.

(3) *Working standard.* Dissolve a weighing of the standard in sufficient ethyl alcohol to give a solution of 10,000 micrograms per milliliter. Further dilute in 1 percent phosphate buffer, pH 6.0, to give a stock solution of 1,000 micrograms per milliliter. This stock solution may be used for 1 month if stored in a refrigerator. The working standard is prepared from the stock solution by diluting a portion with 1 percent phosphate buffer, pH 6.0, to a concentration of 50 micrograms per milliliter.

(4) *Preparation of sample.* Prepare the sample to be tested by dissolving in a small amount of ethyl alcohol and then further dilute in 1 percent phosphate buffer pH 6.0 to make an appropriate stock solution.

(5) *Preparation of suspension.* The test organism is Sarcina lutea (P. C. I.

1001). Maintain the test organism on slants of nutrient agar prepared as in subparagraph (2) of this paragraph and transfer to a fresh agar slant once a week. Prepare a suspension of the test organism as follows: Streak an agar slant heavily with the test organism. Wash the growth off in about 3 milliliters of nutrient broth. Use the suspension so obtained to inoculate the surface of a Roux bottle containing 300 milliliters of the nutrient agar. Spread the suspension over the entire surface with the aid of sterile glass beads. Incubate for 24 hours at 26° C. Wash the growth from the agar surface with 20 milliliters of nutrient broth prepared as in subparagraph (2) of this paragraph. If an aliquot of this bulk suspension, when diluted with nutrient broth 1:10, gives a 10 percent light transmission in a suitable photoelectric colorimeter equipped with a filter having a wave length of 6500 Angstrom units, it is satisfactory for use. It may be necessary to adjust the bulk suspension by dilution so that an aliquot of the adjusted suspension diluted 1:10 gives 10 percent light transmission. (The adjusted bulk suspension only, and not the 1:10 dilution of it, is used in preparing the seed layer.) The bulk suspension may be used in the test for 1 month. Add 1 to 1.5 milliliters of the adjusted bulk suspension to 100 milliliters of agar which has been melted and cooled to 48° C.

(6) *Preparation of plates.* Add 21 milliliters of the agar prepared as in subparagraph (2) of this paragraph to each Petri dish (20 x 100 millimeters). Distribute the agar evenly in the plates and allow it to harden. Use the plates the same day they are prepared. Add 4 milliliters of the inoculum prepared as in subparagraph (5) of this paragraph for each plate, tilting the plates back and forth to spread the inoculated agar evenly over the surface.

(7) *Assay.* Place six cylinders on the inoculated agar surface so that they are at approximatelv 60° intervals on a 2.8-centimeter radius. Use three plates for each sample. Fill three cylinders on each plate with the 50 micrograms per milliliter standard and three cylinders with the 50 micrograms per milliliter (estimated) sample, alternating standard and sample. At the same time, prepare a standard curve by diluting the stock standard solution with 1 percent phosphate buffer, pH 6.0, to give final concentrations of 32.0, 40.0, 50.0, 62.5, and 78.1 micrograms per milliliter. A total of 12 plates is used in the preparation of the standard curve, three plates for each solution except the 50 micrograms per milliliter solution. The latter concentration is used as the reference point and is included on each plate. On each of three plates fill three cylinders with the 50 micrograms per milliliter standard and the other three cylinders with the concentration of the standard under test. Thus, there will be thirty-six 50-microgram determinations and nine determinations for each of the other points on the curve. Incubate the plates for 16 to 18 hours at 32° C.–35° C. and measure the diameter of each circle of inhibition. Average the readings of the 50 micrograms per milliliter concentration and the readings of the point tested for each set of three plates, and average also all 36 readings of the 50 micrograms per milliliter concentration. The average of the 36 readings of the 50 micrograms per milliliter concentration is the correction point for the curve. Correct the average value obtained for each point to the figure it would be if the 50 micrograms per milliliter readings for that set of three plates were the same as the correction point. Thus, if in correcting the 40 micrograms per milliliter concentration the average of the 36 readings of the 50 micrograms per milliliter standard is 18.0 millimeters, and the average of the 50 micrograms per milliliter concentration of this set of plates is 17.8 millimeters, the correction is 0.2 millimeter. If the average reading of the 40 micrograms per milliliter concentration of these same three plates is 17.0 millimeters, the corrected concentration of these same three plates is 17.0 millimeters, the corrected value is then 17.2 millimeters.

Plot these corrected values, including the average of the 50 micrograms per milliliter concentrations on two-cycle semilog paper, using the concentration in micrograms per milliliter as the ordinate (the logarithmic scale) and the diameter of the zone of inhibition as the abscissa. Draw the standard curve through these points. To estimate the potency of the sample, average the zone readings of the standard and the zone readings of the sample on the three plates used. If the sample gives a larger zone size than the average of the standard, add the difference between them to the 50 micrograms per milliliter unit zone on the standard curve. If the average value is lower than the standard value, subtract the difference between them from the 50 micrograms per milliliter unit value on the curve. From the curves read the potencies corresponding to these corrected values of zone sizes.

(8) *Spectrophotometric method.* In lieu of the plate-assay method described, the following method may be used: Dissolve the working standard and the sample to be tested in sufficient water to give solutions containing 20 micrograms per milliliter. Warm if necessary to hasten solution. When cool, determine the absorbance of each solution in a suitable spectrophotometer at 278 mμ compared with distilled water as a blank. Calculate the absorptivity (1%, 1 cm.) as follows:

$$\text{Absorptivity} = \frac{\text{Absorbance at 278 m}\mu \times 1{,}000}{\text{Milligrams of sample (in 100 milliliters)}}.$$

Calculate the potency of the sample as follows:

$$\frac{\text{Absorptivity of sample}}{\text{Absorptivity of standard}} \times 1{,}000 = \text{micrograms of chloramphenicol per milligram.}$$

(9) *Chloramphenicol content.* The potency of chloramphenicol is satisfactory, when assayed by the methods described in this section, if the immediate containers contain 85 percent of the number of grams they are represented to contain.

(b) *Sterility.* Proceed as directed in § 141c.201 (b) of this chapter.

(c) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of a solution containing 2 milligrams per milliliter. Use physiological salt solution as the diluent.

(d) *Pyrogens.* Proceed as directed in § 141a.3 of this chapter, using as a test dose 1.0 milliliter per kilogram of a solution containing 5 milligrams per milliliter. Use physiological salt solution as the diluent.

(e) *Histamine.* Proceed as directed in § 141b.105 of this chapter, using as a test dose 0.6 milliliter per kilogram of a solution containing 5 milligrams per milliliter prepared by application of heat.

(f) *pH.* Proceed as directed in § 141a.5 (b) of this chapter using a saturated aqueous solution.

(g) *Specific rotation.* Accurately weigh approximately 1.25 grams of the sample in a 25-milliliter glass-stoppered volumetric flask and dissolve in about 15 milliliters with absolute alcohol, warming if necessary. Dilute the solution to 25 milliliters with absolute alcohol and mix thoroughly. Transfer the solution to a 200-millimeter tube, determine the angular rotation in a suitable polarimeter, using sodium light or a 5893 Angstrom filter, and calculate the specific rotation.

(h) *Melting point.* Proceed as directed by the U. S. P.

(i) *Absorptivity.* Proceed as directed in paragraph (a)(8) of this section.

§ 141d.302 Chloramphenicol capsules; potency.

(a) *Bioassay method.* Proceed as directed in § 141d.301(a), except subparagraphs (8) and (9) of that paragraph, and in lieu of the directions in subparagraph (4) prepare the sample as follows: Place the contents of not less than 10 capsules and the empty capsules in 100 milliliters of ethyl alcohol, and using a high-speed blender, blend for approximately 2 minutes. To the blender, add 400 milliliters of 1.0-percent phosphate buffer, pH 6.0, and blend for approximately 2 minutes. Withdraw a 1.0-milliliter aliquot and make the proper estimated dilutions in 1.0-percent phosphate buffer, pH 6.0.

(b) *Spectrophotometric assay method.* Place the contents of 10 capsules in a 250-milliliter volumetric flask. Add 50 milliliters of redistilled methanol to the flask and shake for at least 1 minute. Make to volume with distilled water and mix thoroughly. Withdraw an aliquot and dilute with sufficient distilled water to give a concentration of 20 micrograms per milliliter. With a suitable spectrophotometer, determine the optical density of this solution in a 1-centimeter cell at 278 mμ compared with distilled water as a blank.

$$\text{Milligrams per capsule} = \frac{\text{Absorbance of the sample at 278 m}\mu \times \text{labeled potency per capsule in milligrams}}{a_s \times 0.002},$$

where:

a_s is the absorptivity (1%, 1 cm.) of the chloramphenicol standard, similarly treated.

(c) *Chloramphenicol content.* When assayed by either of these methods, its potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chloramphenicol per capsule that it is represented to contain.

§ 141d.303 Chloramphenicol ointment; potency.

Proceed as directed in § 141d.301(a), except § 141d.301(a) (8) and (9), and in lieu of the directions in § 141d.301(a)(4) prepare the sample by one of the following methods:

(a) Place an accurately weighed representative sample (usually 1.0 gram of the ointment) in a blending jar containing 1 milliliter of a 10-percent aqueous solution of polysorbate 80 and sufficient 1-percent phosphate buffer at pH 6.0 to make 100 milliliters. Using a high-speed blender, blend the mixture for 2 minutes and make the proper estimated dilutions in 1-percent phosphate buffer at pH 6.0.

(b) Place a representative sample (0.5 gram) in a separatory funnel containing 10 milliliters of petroleum ether. Shake the separatory funnel vigorously to bring about complete mixing of the ointment and ether. Shake with a 15-milliliter portion of 1-percent phosphate buffer at pH 6.0. Remove the buffer layer and repeat the extraction with two additional 15-milliliter portions of buffer. Combine the extractives and dilute to 50 milliliters with 1-percent phosphate buffer. Make the proper estimated dilutions in 1-percent phosphate buffer at pH 6.0.

The potency of chloramphenicol ointment is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

§ 141d.304 Chloramphenicol ophthalmic.

(a) *Potency.* Proceed as directed in § 141d.301(a), except § 141d.301(a)(9). If the spectrophotometric method is used, calculate as follows:

$$\text{Milligrams per vial} = \frac{\text{Absorbance of the sample at 278 m}\mu \times \text{labeled potency of vial in milligrams}}{a_s \times 0.002},$$

where:

a_s is the absorptivity (1%, 1 cm.) of the chloramphenicol standard, similarly treated.

The potency of chloramphenicol ophthalmic is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a solution prepared as directed in the labeling of the drug.

(c) *Sterility.* Proceed as directed in § 141a.2 of this chapter, except that:

(1) Use 0.5 milliliter of the suspension of the sample prepared according to label directions, and do not use penicillinase or the control tube in the test for bacteria.

(2) In lieu of the last sentence of § 141a.2 (b) of this chapter, the batch meets the requirements of the test for bacteria if no tube shows growth.

(3) In lieu of the last sentence of § 141a.2 (c) of this chapter, the batch meets the requirements of the test for molds and yeasts if no tube shows growth.

§ 141d.305 Chloramphenicol palmitate.

(a) *Potency.* Dissolve 50 milligrams of the sample in absolute ethyl alcohol and make to 100 milliliters in a volumetric flask with absolute ethyl alcohol. Transfer a 5-milliliter aliquot to another 100-milliliter volumetric flask and make to volume with absolute ethyl alcohol. With a suitable spectrophotometer, determine the absorbance of the solution at 271 mμ compared with absolute ethyl alchohol as a blank. Calculate the absorptivity (1%, 1 cm.) of the chloramphenicol working standard similarly prepared but measured at 276 mμ. The potency of the chloramphenicol palmitate, in micrograms of chloramphenicol per milligram of chloramphenicol palmitate, is calculated as follows:

$$\text{Potency} = \frac{\text{Absorptivity of sample at 271 m}\mu \times 1{,}000}{\text{Absorptivity of chloramphenicol standard at 276 m}\mu}.$$

(b) *Toxicity.* Administer orally, by means of a cannula or other suitable device, to each of 5 mice, within the weight range of 18 to 25 grams, 1.0 milliliter of a suspension of the drug containing 60 milligrams per milliliter in 10-percent acacia solution. If no animal dies within 48 hours, the sample is nontoxic. If one or more animals die within 48 hours, repeat the test with 5 unused mice weighing 20 grams (±0.5 gram) each; if all animals survive the repeat test the sample is nontoxic.

(c) *Melting point.* Proceed as directed by the U. S. P.

§ 141d.306 Chloramphenicol palmitate oral suspension.

(a) *Potency.* Transfer an amount of the suspension, equivalent to about 125 milligrams of chloramphenicol, accurately measured, to a separatory funnel. Add 10 milliliters of water and then extract completely with 25-milliliter portions of chloroform, allowing the layers to separate and filtering each successive chloroform extract through a pledget of cotton into a 250-milliliter volumetric flask, then add chloroform to volume, and mix. Pipette 4 milliliters of the clear chloroform solution into a 100-milliliter volumetric flask, dilute with ethyl alcohol to volume, and mix. Using a suitable spectrophotometer, measure the absorbance of the solution at 271 mμ, using as a blank 1.0 milliliter of chloroform U.S.P. diluted to 25 milliliters with absolute ethyl alcohol. The number of milligrams of chloramphenicol contained in each milliliter of cloramphenicol palmitate oral suspension is obtained by the following calculation:

$$\text{Milligrams of chloramphenicol per milliliter} = 62{,}500\left(\frac{A}{aV}\right)$$

where:

A = absorbance of sample at 271 mμ.

a = absorptivity (1%, 1 cm.) of the chloramphenicol working standard in absolute ethyl alcohol measured at 276 mμ.

V = volume, in milliliters, of the suspension taken.

The potency of chloramphenicol palmitate oral suspension is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(b) *pH.* Using the undiluted suspension, proceed as directed in § 141a.5 (b) of this chapter.

§ 141d.307 Chloramphenicol solution; chloramphenicol for aqueous injection.

(a) *Potency*—(1) *Chloramphenicol solution.* Proceed as directed in § 141d.301 (a), except subparagraphs (8) and (9) of that paragraph, and in lieu of the directions in subparagraph (4) of that paragraph dilute the sample in sufficient 1.0-percent phosphate buffer pH 6.0 to make an appropriate stock solution.

(2) *Chloramphenicol for aqueous injection.* Proceed as directed in § 141d.301 (a), except subparagraph (9) of that paragraph, and in lieu of the directions in subparagraph (4) of that paragraph prepare the sample as follows: Add the amount of water indicated in the labeling of the drug to the vial, and shake well. Remove 1.0 milliliter of the suspension, transfer to a 50-milliliter volumetric flask, and make to volume with absolute alcohol. Quickly remove 1.0 milliliter and make to the proper estimated dilution in 1.0-percent phosphate buffer pH 6.0. In case the spectrophotometric method is used, proceed as follows: Add to the vial the amount of water indicated in the labeling of the drug and shake vigorously until a uniform suspension is obtained. Transfer one dose of this suspension to a 1,000-milliliter glass-stoppered volumetric flask, add about 500 milliliters of distilled water and heat on a steam bath until solution of the chloramphenicol is complete (but no longer than 10 minutes). Cool to room temperature and dilute to exactly 1,000 milliliters with distilled water. Mix thoroughly and volumetrically dilute an aliquot of this solution with distilled water to obtain a solution containing 20 micrograms per milliliter (estimated). Measure the absorbance of this solution in a suitable spectrophotometer at 278 $m\mu$ against a blank of distilled water.

$$\text{Grams of chloramphenicol in the sample tested} = \frac{\text{Absorbance of sample at 278 m}\mu \times 10 \times F}{a_s}$$

where:

F = the appropriate dilution factor.

a_s = absorptivity (1%, 1 cm.) of the chloramphenicol working standard in distilled water measured at 278 $m\mu$.

From this value calcuate the quantity of chloramphenicol in the immediate container.

Its potency is satisfactory when assayed by the methods described in this paragraph if it contains not less than 85 percent of the number of grams of chloramphenicol it is represented to contain.

(b) *Sterility.* If it is the solution, proceed as directed in § 141b.102 of this chapter. If it is the dry mixture of the drug, dissolve the entire contents of each vial to be tested in a sterile 40-percent solution (v/v) of N,N,dimethylacetamide, using 10 milliliters of the diluent for each 1.0 gram, and proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Toxicity.* Proceed as directed in § 141d.301 (c).

(d) *Pyrogens.* Proceed as directed in § 141d.301 (d).

(e) *Histamine.* Proceed as directed in § 141d.301 (e).

(f) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using the undiluted drug in the case of the solution, and if it is the dry mixture of the drug use a suspension prepared as directed in its labeling.

§ 141d.308 Chloramphenicol otic; chloramphenicol topical.

(a) *Potency.* Using 1.0 milliliter, proceed as directed in § 141d.303(a). Its potency is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c) of this chapter.

(c) *pH.* Dilute the drug with an equal volume of distilled water and proceed as directed in § 141a.5 (b) of this chapter.

§ 141d.309 Chloramphenicol-streptomycin capsules; chloramphenicol-dihydrostreptomycin capsules.

(a) *Potency*—(1) *Content of chloramphenicol.* Proceed as directed in § 141d.302 (a) or (b). Its content of chloramphenicol is satisfactory if it contains not less than 85 percent of the number of milligrams per capsule that it is represented to contain.

(2) *Content of streptomycin.* Using 10 capsules, proceed as directed in § 141b.101 of this chapter, except paragraphs (j) and (k) of that section. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per capsule that it is represented to contain.

(3) *Content of dihydrostreptomycin.* Proceed as directed in subparagraph (2) of this paragraph, using the dihydrostreptomycin working standard as a standard of comparison. Its content of dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per capsule that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141d.310 Chloramphenicol tablets.

(a) *Bioassay method.* Proceed as directed in § 141d.302 (a).

(b) *Spectrophotometric assay method.* Weigh accurately a counted number of not less than 10 tablets and determine the average weight per tablet. Reduce 10 tablets to a fine powder in a mortar and transfer an amount of powder containing 500 milligrams (estimated) of chloramphenicol to a 1,000-milliliter glass-stoppered volumetric flask. Add 50 milliliters of redistilled methanol to the flask and shake for at least 1 minute. Make to volume with distilled water and mix thoroughly. Transfer exactly 10 milliliters of this solution into a 250-milliliter glass-stoppered volumetric flask. Make to mark and mix thoroughly. Determine the absorbance of this solution on a suitable spectrophotometer in a 1-centimeter quart cell at 278 $m\mu$ against a blank of distilled water.

$$\text{Milligrams of chloramphenicol per tablet} = \frac{\text{Absorbance of the sample} \times \text{average weight of tablet in milligrams} \times 250{,}000}{a_s \times \text{weight of powder tested in milligrams}}$$

where:

a_s = the absorptivity (1%, 1 cm.) of the chloramphenicol working standard measured at 278 $m\mu$.

(c) *Chloramphenicol content.* When assayed by either of these methods, its potency is satisfactory if it contains not less than 85 percent of the number of milligrams of chloramphenicol per tablet that it is represented to contain.

(d) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141d.311 Chloramphenicol palmitate-streptomycin oral suspension; chloramphenicol palmitate-dihydrostreptomycin oral suspension.

(a) *Potency*—(1) *Chloramphenicol content.* Proceed as directed in § 141d.306(a). Its content of chloramphenicol is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Steptomycin or dihydrostreptomycin content.* Proceed as directed in § 141b.101 of this chapter except § 141b.101 (b), and if it contains dihydrostreptomycin use the dihydrostreptomycin working standard as the standard of comparison. Its content of streptomycin or dihydrostreptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *pH.* Using the undiluted suspension, proceed as directed in § 141a.5 (b) of this chapter.

§ 141d.312 Chloramphenicol-neomycin ointment.

(a) *Potency* — (1) *Chloramphenicol content.* Proceed as directed in § 141d.303. Its content of chloramphenicol is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(2) *Neomycin content.* Place an accurately weighed representative sample (usually 1.0 gram of ointment) in a separatory funnel containing 50 milliliters of peroxide-free diethyl ether. Shake the sample and ether until homogeneous.

Add 25 milliliters of 0.1 *M* potassium phosphate buffer, pH 8.0, and shake. Allow the layers to separate. Remove the buffer layer and repeat the extraction at least three times with additional portions of buffer and any additional times necessary to insure complete extraction. Make the proper estimated dilution with buffer and proceed as directed in § 141e.410 (b) (1) of this chapter. Its content of neomycin is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.7 (c) of this chapter.

§ 141d.313 Chloramphenicol-polymyxin ointment; potency.

(a) *Chloramphenicol content.* Proceed as directed in § 141d.303. Its chloramphenicol content is satisfactory if it contains not less than 85 percent of the number of milligrams per gram that it is represented to contain.

(b) *Polymyxin content.* Proceed as directed in § 141b.112 (b) (1) of this chapter, except in lieu of the directions in § 141b.112 (b) (1) (vii) of this chapter for the preparation of the sample, prepare the sample as follows: Place an accurately weighed sample (usually approximately 1.0 gram) in a separatory funnel containing approximately 50 milliliters of peroxide-free ether, and shake the sample and ether until homogeneous. Add 25 milliliters of 10-percent potassium phosphate buffer, pH 6.0, and shake. Remove the buffer layer and repeat the extraction with three additional 25-milliliter portions of buffer. Combine the extractives and make the proper estimated dilutions, using the buffer solution, except that, if the sample contains a water-soluble base, place an accurately weighed representative sample in a blending jar containing 1.0 milliliter of polysorbate 80 and sufficient 10 percent potassium phosphate buffer, pH 6.0, to give a final volume of 200 milliliters. Using a high-speed blender, blend the mixture for 2 minutes to 3 minutes and then make the proper estimated dilutions with 10 percent phosphate buffer, pH 6.0. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units per gram that it is represented to contain.

§ 141d.314 Chloramphenicol sodium succinate.

(a) *Potency (by spectrophotometric assay)*—(1) *Working standard.* Prepare the standard stock solution by dissolving an appropriate amount (accurately weighed) of the chloramphenicol working standard in sterile distilled water to give a solution containing 20 μg per milliliter. Using a suitable spectrophotometer, determine the absorbance of the solution in a 1-centimeter cell at 278 mμ compared with distilled water as a blank. Calculate the absorptivity (1%, 1 cm.) as follows:

$$a=\frac{\text{Absorbance at 278 m}\mu}{\text{Grams of standard per 100 milliliters}}.$$

(2) *Procedure.* Dissolve the sample to be tested in sufficient sterile distilled water to give a solution containing 30 μg. per milliliter. Using a suitable spectrophotometer, determine the absorbance of the solution in a 1-centimeter cell at 276 mμ compared with distilled water as a blank. Calculate the absorptivity as follows:

$$a=\frac{\text{Absorbance at 276 m}\mu}{\text{Grams of sample per 100 milliliters}}.$$

Calculate the potency of the sample as follows:

$$\frac{a \text{ of sample}}{a \text{ of standard}}\times 1{,}000=\text{Micrograms of chloramphenicol per milligram of chloramphenicol sodium succinate.}$$

(b) *Sterility.* Using 40 milligrams from each container tested, proceed as directed in § 141a.2 of this chapter, except that neither penicillinase nor the control tube is used in the test for bacteria.

(c) *Toxicity.* Use sterile physiological salt solution as the diluent, and proceed as directed in § 141a.4 of this chapter, using as a test dose 0.5 milliliter of a solution containing 2 milligrams of chloramphenicol activity per milliliter.

(d) *Pyrogens.* Use sterile physiological salt solution as the diluent and proceed as directed in § 141a.3 of this chapter, using as a test dose 1.0 milliliter per kilogram, of a solution containing 5 milligrams of chloramphenicol activity per milliliter.

(e) *Histamine.* Proceed as directed in § 141b.105 of this chapter, using as a test dose 0.6 milliliter per kilogram of a solution containing 5 milligrams of chloramphenicol activity per milliliter.

(f) *Moisture.* Proceed as directed in § 141a.26(e) of this chapter.

(g) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using an aqueous solution containing 200 milligrams per milliliter.

(h) *Specific rotation.* Accurately weigh the sample to be tested in a volumetric flask and dilute with sufficient distilled water to give a solution containing approximately 50 milligrams per milliliter. Transfer the solution to a tube of 1-decimeter length and determine the angular rotation in a suitable polarimeter, using sodium light or a 589.3-mμ filter, and calculate the specific rotation.

§ 141d.315 Chloramphenicol sodium succinate for aqueous injection.

(a) *Potency.* Dissolve the entire contents of each vial to be tested in the minimum volume of distilled water recommended in the labeling, withdraw the entire removable contents and further dilute with sufficient distilled water to give a concentration of 20 μg. per milliliter of chloramphenicol (estimated). With a suitable spectrophotometer, determine the absorbance of this solution in a 1-cm. cell at 276 mμ compared with distilled water as a blank. Also determine the absorptivity (1%, 1 cm.) at 278 mμ of an aqueous solution of the chloramphenicol standard containing exactly 20 μg. per milliliter.

$$\text{Potency per vial}=\frac{\text{Absorbance of sample}\times 500\times\text{labeled potency of vial}}{\text{Absorptivity of standard}}.$$

Its potency is satisfactory if it contains not less than 90 percent of the chloramphenicol activity that it is represented to contain.

(b) *Sterility.* Proceed as directed in § 141d.314(b).

(c) *Toxicity.* Proceed as directed in § 141d.314(c).

(d) *Pyrogens.* Proceed as directed in § 141d.314(d).

(e) *Histamine.* Proceed as directed in § 141d.314(e).

(f) *Moisture.* Proceed as directed in § 141d.314(f).

(g) *pH.* Proceed as directed in § 141d.314(g).

§ 141d.316 Chloramphenicol-paromomycin ointment.

(a) *Potency*—(1) *Chloramphenicol content*—(i) *Microbiological assay.* Proceed as directed in § 141d.303.

(ii) *Chemical assay*—(a) *Hydrocortisone standard.* Dissolve an accurately weighed sample of hydrocortisone acetate (30 milligrams to 50 milligrams) in sufficient methyl alcohol to give a concentration of 1 milligram per milliliter. Remove a suitable aliquot and dilute to a concentration of 20 micrograms per milliliter, using methyl alcohol. Determine the absorbance at 242 mμ and 274 mμ, respectively, and calculate the absorptivities, $^{*}hc242$, $^{*}hc274$.

(b) *Chloramphenicol standard.* Dissolve an accurately weighted sample (30 milligrams to 50 milligrams) of the chloramphenicol working standard in sufficient methyl alcohol to give a concentration of 1 milligram per milliliter. Remove a suitable aliquot and dilute to a concentration of 20 micrograms per milliliter, using methyl alcohol. Determine the absorbance of 242 mμ and 274 mμ, respectively, and calculate the absorptivities, $^{*}ch242$, $^{*}ch274$.

(c) *Sample for assay.* Place the sample to be tested (approximately 1.0 gram of ointment, accurately weighed) into a 500-milliliter volumetric flask. Add 20 milliliters of cyclohexane and agitate until the ointment is thoroughly dispersed. Add 200 milliliters of methyl alcohol and mix. Make to mark with methyl alcohol. Mix well. Remove a suitable portion and centrifuge until clear. Determine its absorbance at 242 mμ and 274 mμ ($A242$, $A274$) against a blank prepared by diluting 2.0 milliliters of cyclohexane with methyl alcohol to give 50 milliliters. Read in a suitable spectrophotometer in a 1-centimeter cell, and calculate as follows:

$$\text{Hydrocortisone content (\% weight/weight)} = \frac{[(^{s}ch274)(A242)-(^{s}ch242)(A274)]\times 5\times 100}{[(^{s}hc242)(^{s}ch274)-(^{s}hc274)(^{s}ch242)]} \times \text{weight of sample in grams}$$

and

$$\text{Chloramphenicol content (\% weight/weight)} = \frac{[(^{s}hc242)(A274)-(^{s}hc274)(A242)]\times 5\times 100}{[(^{s}ch274)(^{s}hc242)-(^{s}ch242)(^{s}hc274)]} \times \text{weight of sample in grams}$$

where:

$^{s}hc242$ = absorptivity (1 cm., 1%) of hydrocortisone standard at 242 mμ.
$^{s}hc274$ = absorptivity (1 cm., 1%) of hydrocortisone standard at 274 mμ.
$^{s}ch242$ = absorptivity (1 cm., 1%) of chloramphenicol standard at 242 mμ.
$^{s}ch274$ = absorptivity (1 cm., 1%) of chloramphenicol standard at 274 mμ.
$A242$ = absorbance of sample at 242 mμ.
$A274$ = absorbance of sample at 274 mμ.

When assayed by either of the above methods, its chloramphenicol content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(2) *Paromomycin content.* Proceed as directed in paragraph (b)(1) of this section, except prepare the sample as follows: Place an accurately weighed representative sample (usually 1.0 gram of the ointment) in a blending jar containing 1 milliliter of concentrated polysorbate 80 and 248 milliliters of 0.1 *M* potassium phosphate buffer (pH 8.0). Using a high-speed blender, blend the mixture for 2 minutes and make the proper estimated dilutions in 0.1 *M* potassium phosphate buffer, pH 8.0. Its paromomycin content is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Paromomycin sulfate used in making the ointment*—(1) *Potency.* (i) Proceed as directed in § 141c.231(c)(1) of this chapter, except that:

(*a*) In lieu of the directions in § 141c.231(c)(1)(iii) of this chapter, prepare the standard as follows: Dissolve a suitable weighed quantity (usually 25 milligrams or less) of the working standard in sufficient 0.1 *M* potassium phosphate buffer, pH 8.0, to give a concentration of 1,000 micrograms of paromomycin per milliliter. This stock solution may be kept in the refrigerator for 3 weeks.

(*b*) In lieu of the directions in § 141c.231(c)(1)(iv) of this chapter, dilute the sample to a final concentration of 1.0 microgram per milliliter (estimated).

(*c*) In lieu of the concentrations for the standard curve as prescribed in § 141c.231(c)(1)(vii) of this chapter, prepare concentrations of 0.64, 0.80, 1.00, 1.25, and 1.56 micrograms per milliliter. The 1.00 microgram per milliliter solution is the reference concentration.

(ii) As an alternative method, proceed as directed in § 141b.101 (a) through (i) of this chapter, except that:

(*a*) In lieu of the directions in § 141b.101(b) of this chapter, prepare the nutrient agar for the base and seed layers as follows:

Beef extract	6.0 gm.
Peptone	10.0 gm.
Agar	15.0 gm.
Distilled water q.s.	1,000.0 ml.

pH 7.8–8.0 after sterilization.

(*b*) Prepare the standard stock solution as described in subdivision (i)(*a*) of this subparagraph, and in lieu of the concentrations for the standard curve as prescribed in § 141b.101(d) of this chapter, prepare concentrations of 1.28, 1.6, 2.0, 2.5, and 3.12 micrograms per milliliter from this stock solution and use the 2.0 micrograms per milliliter concentration as the reference point.

(*c*) In lieu of the directions in § 141b.101(e) of this chapter, dilute the sample to a final concentration of 2.0 micrograms per milliliter (estimated).

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using a 3.0 percent aqueous solution.

(3) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(4) *Specific rotation.* Accurately weigh approximately 1.25 grams of the sample into a 25-milliliter volumetric flask. Dissolve in a few milliliters of water, add water to volume, and mix. Transfer the solution to a 200-millimeter tube, determine the angular rotation in a suitable polarimeter, using a sodium light or 5893 Angstrom filter, and calculate the specific rotation.

(5) *Ash content.* Place a 1-gram sample in a tared, heavy, metal-free evaporating dish, and add 2 milliliters of concentrated H_2SO_4. Completely char on low flame, raising the temperature gradually until fumes of SO_3 disappear. Ignite at dull-red heat or in a muffle furnace at 1,100° F.

PART 141e—BACITRACIN AND BACITRACIN-CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

Sec.
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141e.410 Bacitracin-neomycin tablets; zinc bacitracin-neomycin tablets; bacitracin methylene disalicylate-neomycin tablets.
141e.411 Bacitracin-neomycin ointment; zinc bacitracin-neomycin ointment.
141e.412 Bacitracin-polymyxin tablets.
141e.413 Bacitracin-neomycin troches; zinc bacitracin-neomycin troches.
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141e.420 Bacitracin - tyrothricin - neomycin troches; bacitracin-gramicidin-neomycin troches; zinc bacitracin-tyrothricin-neomycin troches; zinc bacitracin-gramicidin-neomycin troches.
141e.421 Bacitracin - neomycin - polymyxin tablets.
141e.422 Bacitracin - polymyxin - neomycin ointment.
141e.423 Soluble bacitracin methylene disalicylate.
141e.424 Bacitracin - neomycin - polymyxin with vasoconstrictor.
141e.425 Bacitracin powder.
141e.426 Tablets bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.
141e.427 Feed grade bacitracin powder oral veterinary; (crude bacitracin powder oral veterinary; unrefined bactracin powder oral veterinary); feed grade zinc bacitracin powder oral veterinary (crude zinc bacitracin powder oral veterinary, unrefined zinc bactracin powder oral veterinary).
141e.428 Capsules bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.
141e.429 Bacitracin-neomycin in oil veterinary.
141e.430 Bacitracin - neomycin - polymyxin powder topical; zinc bacitracin-neomycin-polymyxin powder topical.
141e.431 Feed grade manganese bacitracin powder oral veterinary.

AUTHORITY: §§ 141e.401 to 141e.431 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 141e.401 Bacitracin.

(a) *Potency*—(1) *Plate assay.* Using the standard curve technique, proceed as directed in § 141a.1(h) of this chapter, with the following exceptions:

(i) Dry the working standard (obtained from the Food and Drug Administration) for 3 hours at 60° C. under 5 millimeters or less pressure. Weigh a sufficient amount to make a convenient stock solution and dilute in 1 percent phosphate buffer, pH 6.0. The stock solution when refrigerated may be used for two weeks. The stock solution may also be preserved for at least two months by freezing in small aliquots. Each aliquot should be sufficient for 1 day's use only. Make all dilutions of the stock solution for the assay with 1 percent phosphate buffer.

(ii) Dissolve the sample to be tested in 1-percent phosphate buffer and make dilutions with the same solvent to one unit per milliliter (estimated).

(iii) The test organism is either *Micrococcus flavus* (ATCC 10240) or *Sarcina subflava* (ATCC 7468), both of which are maintained at refrigerator temperature on slants of nutrient agar prepared as directed in § 141a.1(b)(1) of this chapter. Inoculate a Roux bottle containing this agar from a stock slant of the organism and incubate 18 hours at

32° C.–35° C. Wash off the growth in 25 milliliters of sterile sodium chloride solution. If an aliquot of this bulk suspension, when diluted 1:50 in sodium chloride solution, gives 75 percent light transmission, if it is *Micrococcus flavus* (ATCC 10240), or 50 percent light transmission, if it is *Sarcina subflava* (ATCC 7468) in a suitable photoelectric colorimeter equipped with a filter having a wavelength of 6,500 Angstrom units, the bulk suspension is satisfactory for use. It may be necessary to adjust the bulk suspension by dilution so that an aliquot of the adjusted suspension diluted 1:50 gives 75 percent light transmission, if it is *Micrococcus flavus* (ATCC 10240) or 50 percent light transmission if it is *Sarcina subflava* (ATCC 7468). (The adjusted bulk suspension only, and not the 1:50 dilution of it, is used in preparing the seed layer.) Add 0.3 to 0.5 milliliter of the adjusted bulk suspension to 100 milliliters of agar that has been melted and cooled to 48° C.

(2) *Turbidimetric assay.* In lieu of the plate-assay method described above, the sample may be assayed for potency by the following turbidimetric method:

(i) *Test culture and media.* The test organism is *Staphylococcus aureus* (ATCC 10537), which is maintained at refrigerator temperature on slants of nutrient agar prepared as directed in § 141.a1(b)(1) of this chapter. Inoculate a Roux bottle containing this agar from a stock slant of the organism and incubate 18 hours at 32° C.–35° C. Wash off the growth in 50 milliliters of sterile sodium chloride solution. If an aliquot of the bulk suspension, when diluted 1:10 in sodium chloride solution, gives 20 percent light transmission in a suitable photoelectric colorimeter equipped with a filter having a wavelength of 6,500 Angstrom units, the bulk suspension is ready for use. It may become necessary to adjust the bulk suspension by dilution so that an aliquot of the adjusted suspension diluted 1:10 gives 20 percent light transmission. (The adjusted suspension only, and not the 1:10 dilution, is used in preparing the daily inoculum.) Prepare the daily inoculum by adding approximately 0.2 milliliter of the adjusted suspension to each 100 milliliters of refrigerated broth.

(ii) *Working standard solutions.* Dilute the working standard to 10 units per milliliter of bacitracin in 1 percent phosphate buffer. Further dilute this to make solutions containing 0.256, 0.320, 0.400, 0.500, and 0.625 units per milliliter. These solutions are used for preparing the standard curve and may be held under refrigeration for 1 week. Add 1.0 milliliter of each of these working standard solutions to each of three 16 millimeter x 125 millimeter tubes (outside dimension).

(iii) *Preparation of sample.* Dilute the sample under test to 0.400 unit per milliliter (estimated). Add 1.0 milliliter of the diluted sample to each of three 16 millimeter x 125 millimeter tubes (outside dimension). Add 9.0 milliliters of the "daily" inoculum described in subdivision (i) of this subparagraph to each tube of the standard and unknown series and place immediately in a 37° C. water bath for 4 hours. After incubation, add four drops of formaldehyde to each tube, and estimate the turbidity of each in a photoelectric colorimeter, using a broad-band filter having a wavelength of 5300 Angstrom units.

(iv) *Estimation of potency.* Average the three colorimeter readings at each standard level. Plot the average absorbance figures of the standard on semilog graph paper, employing units per tube as the logarithmic scale and absorbance as the arithmetic scale. Connect the points with a straightedge. Average the sample readings and read in units per tube from the curve. Units per tube divided by 0.400×100 will give percent potency of the sample.

(3) *Bacitracin content.* The potency of bacitracin is satisfactory when assayed by the methods described in this section if the immediate containers contain not less than 85 percent and, if it is intended for systemic medication, not more than 115 percent of the number of units they are represented to contain.

(b) *Sterility.* Proceed as directed in § 141b.102 of this chapter.

(c) *Pyrogens.* Proceed as directed in § 141a.3 of this chapter, using as a test dose 1.0 milliliter per kilogram of a solution containing 300 units per milliliter. Use physiological salt solution as the diluent.

(d) *Toxicity.* Inject intravenously each of five mice within the weight range of 18–25 grams with 0.5 milliliter of a solution of the sample prepared by diluting with sterile physiological salt solution to 200 units per milliliter. The injection should be made over a period of not more than 5 seconds. If no animal dies within 48 hours, the sample is nontoxic. If one or more animals die within 48 hours, repeat the test with five unused mice weighing 20 grams (±0.5 gram) each. If all animals survive the repeat test the sample is nontoxic.

(e) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(f) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a solution containing 10,000 units per milliliter.

(g) *Ash content.* Place approximately 1 gram of the sample, accurately weighed, in a tared porcelain crucible and carefully ignite at a low temperature until thoroughly charred. The crucible may be loosely covered with a porcelain lid during the charring. Add to the contents of the crucible 2 milliliters of nitric acid and 5 drops of sulfuric acid, and cautiously heat until white fumes are evolved, then ignite, preferably in a muffle furnace, at 500° C. to 600° C. until the carbon is all burned off. Cool the crucible in a desiccator and weigh. From the weight of residue obtained, calculate the sulfated ash content.

(h) *Heavy metals content.* Using the sulfated ash obtained in paragraph (g) of this paragraph, proceed as directed in the U. S. P. Heavy Metals Test, Method II, starting with the words "Cool, add 2 ml. of hydrochloric acid * * *."

§ 141e.402 Bacitracin ointment; zinc bacitracin ointment.

(a) *Potency.* If it is bacitracin, proceed as directed in § 141e.401(a), except § 141e.401(a)(3), and in lieu of the directions in § 141e.401(a)(1)(ii), prepare the sample as directed in § 141a.8(a) of this chapter. If it is zinc bacitracin, use 0.01 *N* HCl in lieu of 1-percent phosphate buffer, pH 6.0, for the extraction or blending operation, and in lieu of the directions in § 141e.401(a)(1)(i), prepare the standard as follows. Prepare the stock solution as directed in § 141e.401(a)(1)(i), except that the dilutions for assay are prepared to contain the same ratio of 0.01 *N* HCl to 1-percent phosphate buffer, pH 6.0, as the sample under test. Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b) of this chapter.

§ 141e.403 Bacitracin tablets; zinc bacitracin tablets; bacitracin methylene disalicylate tablets.

(a) *Potency.* Proceed as directed in § 141e.401(a), except § 141e.401(a)(3), and in addition to the directions in § 141e.401(a)(1)(ii), proceed as follows: If it is bacitracin, place a representative sample (usually 5 tablets) in a blending jar containing 250 milliliters of 1-percent phosphate buffer, pH 6.0 If it is zinc bacitracin, use 250 milliliters of 0.01 *N* HCl, and if it is bacitracin methylene disalicylate, use 99 milliliters of an aqueous solution of 2-percent sodium bicarbonate and 1 milliliter of polysorbate 80. If it is bacitracin, after blending for 1 minute with a high-speed blender, add 250 milliliters of buffer to the blender, and if it is zinc bacitracin, add 250 milliliters of 0.01 *N* HCl to the blender. Blend again for 1 minute and make the proper estimated dilutions in 1-percent phosphate buffer, pH 6.0. If it is zinc bacitracin, in lieu of the directions in § 141e.401(a)(1)(i) prepare the standard as follows: Using the stock solution described in § 141e.401(a)(1)(i), make all dilutions for the assay so that the final dilution contains the same ratio of 0.01 *N* HCl to 1-percent phosphate buffer, pH 6.0, as the sample under test. The content of bacitracin, zinc bacitracin, or bacitracin methylene disalicylate is satisfactory if it contains not less than 85 percent of the number of units per tablet that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141e.404 Bacitracin troches; zinc bacitracin troches.

(a) *Potency.* If it is bacitracin, dissolve 5 troches in a small amount of 1 percent phosphate buffer, pH 6.0, then add sufficient buffer to give a volume of 100 milliliters and proceed as directed in § 141e.401(a)(1). If it is zinc bacitracin, dissolve 5 troches in sufficient 0.01 *N* HCl to give a concentration of 10 units per milliliter (estimated) and proceed as directed in § 141e.401(a)(1), except § 141e.401(a)(1)(i). If the troches are composed of a water-insoluble base, use a mortar and pestle and grind to a fine powder before adding the

acid, and in lieu of the directions in § 141e.401(a)(1)(i), prepare the standard as follows: Prepare the stock solution as directed in § 141e.401(a)(1)(i), except that the dilutions for assay are prepared to contain the same ratio of 0.01 *N* HCl to 1-percent phosphate buffer, pH 6.0, as the sample under test. The average potency of the troche is satisfactory if it is not less than 85 percent of the number of units per troche that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.405 Bacitracin with vasoconstrictor.

(a) *Potency.* Prepare the drug as directed in its labeling and proceed as directed in § 141e.401(a), except § 141e.401(a)(3). The potency of bacitracin with vasoconstrictor is satisfactory if it contains not less than 85 percent of the number of units per container it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a solution prepared as directed in the labeling of the drug.

§ 141e.406 Bacitracin-tyrothricin troches; zinc bacitracin-tyrothricin troches.

(a) *Potency.* Proceed as directed in § 141e.404(a). Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units per troche that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.407 Bacitracin-tyrothricin ointment.

Proceed as directed in § 141e.402. Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units per gram it is represented to contain.

§ 141e.408 Bacitracin ophthalmic.

(a) *Potency.* Proceed as directed in § 141e.401(a).

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(c) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using a solution prepared as directed in the labeling for the drug.

(d) *Sterility.* Proceed as directed in § 141a.2 of this chapter, except that:

(1) Do not use penicillinase or the control tube in the test for bacteria.

(2) In lieu of the last sentence of § 141a.2(b) of this chapter, the batch meets the requirements of the test for bacteria if no tube shows growth.

(3) In lieu of the last sentence of § 141a.2(c) of this chapter, the batch meets the requirements of the test for molds and yeasts if no tube shows growth.

§ 141e.409 Bacitracin-polymyxin ointment; zinc bacitracin-polymyxin ointment.

(a) *Potency*—(1) *Bacitracin or zinc bacitracin content.* Proceed as directed in § 141e.402(a). Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units per gram that it is represented to contain.

(2) *Polymyxin content.* Proceed as directed in § 141b.112(b)(1) of this chapter, except in lieu of the directions in § 141b.112(b)(1)(vii) for the preparation of the sample, prepare the sample by one of the following methods: Accurately weigh approximately 5 grams and transfer to a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake with four 25-milliliter portions of 10-percent potassium phosphate buffer (pH 6.0) and combine the extracts. However, if the ointment contains a water-soluble base, accurately weigh approximately 5 grams and place in a blending jar containing 1.0 milliliter of polysorbate 80 and sufficient 10 percent potassium phosphate buffer, pH 6.0, to give a final volume of 200 milliliters. Using a high-speed blender, blend the mixture for 2 minutes and then make the proper estimated dilutions using 10 percent phosphate buffer, pH 6.0. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units per gram that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141e.410 Bacitracin-neomycin tablets; zinc bacitracin-neomycin tablets; bacitracin methylene disalicylate-neomycin tablets.

(a) *Tablets*—(1) *Potency*—(i) *Bacitracin, zinc bacitracin, or bacitracin methylene disalicylate content.* Proceed as directed in § 141e.403(a). Its content of bacitracin, zinc bacitracin, or bacitracin methylene disalicylate is satisfactory if it contains not less than 85 percent of the number of units per tablet that it is represented to contain.

(ii) *Neomycin content.* Place 5 tablets in a blending jar and add thereto 200 milliliters of a 500-milliliter quantity of 0.10-percent phosphate buffer pH 8.0. After blending for 1 minute with a high-speed blender, add the remainder of the buffer. Blend again for 1 minute and make the proper estimated dilutions in the buffer and proceed as directed in paragraph (b)(1) of this section. Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams of activity that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 141a.9(c).

(b) *Neomycin used in making the tablets*—(1) *Potency*—(i) *Cylinders (cups).* Use cylinders described under § 141a.1(a) of this chapter.

(ii) *Culture medium.* Use the medium described in § 141a.1(b)(1) of this chapter for both the base and seed layers, except its pH after sterilization is 7.8 to 8.0.

(iii) *Working standard.* Dry the working standard (obtained from the U. S. P. Reference Standards Committee, 46 Park Avenue, New York 16, N. Y.) for 3 hours at 60° C. and a pressure of 5 millimeters or less and weigh out a sufficient quantity to make a convenient stock solution by diluting with a 0.1 *M* potassium phosphate buffer, pH 7.8 to 8.0. The stock solution, when stored at a temperature of approximately 15° C., or less, may be used for a period not exceeding 1 month.

(iv) *Standard curve.* Using the stock solution, prepare a daily standard curve as directed in § 141b.101(d) of this chapter, using solutions of the neomycin working standard in 0.1 *M* potassium phosphate buffer, pH 8.0, in concentrations of 6.4, 8.0, 10.0, 12.5, and 15.6 micrograms per milliliter if the test organism Staphylococcus aureus (ATCC 6538P), or in concentrations of 0.64, 0.80, 1.0, 1.25, and 1.56 micrograms per milliliter if the test organism is Staphylococcus epidermidis (ATCC 12228). The 10.0 micrograms per milliliter and the 1.0 microgram per milliliter concentrations are used as the reference points.

(v) *Preparation of test organism.* The test organism is Staphylococcus aureus (ATCC 6538P), which is maintained on agar described in § 141a.1(b)(1) of this chapter. From a stock slant inoculate a Roux bottle containing this same agar and incubate for 24 hours at 32° C.–35° C. Wash the resulting growth from the agar surface with about 50 milliliters of sterile sodium chloride solution. Standardize this suspension by determining the dilution that will permit 80 percent light transmission through a filter at 6500 Angstrom units in a photoelectric colorimeter. The suspension may be used for 2 weeks if it is stored under refrigeration. Staphylococcus epidermidis (ATCC 12228), which is maintained on agar as described in § 141a.1(b)(1) of this chapter, may also be used as the test organism. From a stock slant, inoculate a Roux bottle containing this medium and incubate for 24 hours at 32° C.–35° C. Wash the resulting growth from the agar surface, using approximately 30 milliliters of sterile sodium chloride solution. Standardize the suspension by determining the dilution that will permit 80 percent light transmission through a filter of 6500 Angstrom units in a photoelectric colorimeter. The suspension may be stored for 2 weeks under refrigeration.

(vi) *Preparation of plates.* Using the agar described in subdivision (ii) of this subparagraph and approximately a 0.5 percent inoculum of the suspension described in subdivision (v) of this subparagraph, prepare the plates as directed in § 141a.1(e) of this chapter.

(vii) *Assay.* Dissolve volumetrically in 0.1 *M* potassium phosphate buffer, pH 7.8 to 8.0, the sample to be tested to make a convenient stock solution. Further dilute volumetrically this solution with 0.1 *M* potassium phosphate buffer, pH 7.8 to 8.0, to a final concentration of 10.0 micrograms (estimated) per milliliter, if the test organism is Staphylococcus aureus or 1.0 microgram per milliliter (estimated) if the test organism is Staphylococcus epidermidis.

(2) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using 0.5 milliliter of a solution prepared by diluting the sample to approximately 200 micrograms per milliliter with physiological salt solution.

(3) *Moisture.* In an atmosphere of about 10 percent relative humidity, transfer about 100 milligrams of the finely powdered sample to a tared weighing bottle equipped with ground-glass top and stopper. Weigh the bottle and place it in a vacuum oven, tilting the stopper on its side so that there is no closure during the drying period. Dry at a temperature of 60° C. and a pressure of 5 millimeters of mercury or less for 3 hours. At the end of the drying period fill the vacuum oven with air dried by passing it through a drying agent such as sulfuric acid or silica gel. Replace the stopper and place the weighing bottle in a desiccator over a desiccating agent such as phosphorous pentoxide or silica gel, allow to cool to room temperature, and reweigh. Calculate the percent loss.

(4) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using a solution containing 33 milligrams per milliliter.

§ 141e.411 Bacitracin-neomycin ointment; zinc bacitracin-neomycin ointment.

(a) *Potency*—(1) *Bacitracin or zinc bacitracin content.* Proceed as directed in § 141e.402(a). Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units per gram that it is represented to contain.

(2) *Neomycin content.* Prepare the sample as directed in § 141a.8(a) of this chapter, except in lieu of potassium phosphate buffer use 0.10 *M* phosphate buffer (pH 7.8–8.0) and proceed as directed in § 141e.410(b)(1). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

§ 141e.412 Bacitracin-polymyxin tablets.

(a) *Potency*—(1) *Bacitracin content.* Proceed as directed in § 141e.403(a). Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units it is represented to contain.

(2) *Polymyxin content.* Using 10-percent potassium phosphate buffer, pH 6.0, prepare the sample as directed in subparagraph (1) of this paragraph, and proceed as directed in § 141b.112 (b) of this subchapter. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141e.413 Bacitracin-neomycin troches; zinc bacitracin-neomycin troches.

(a) *Potency*—(1) *Content of bacitracin and zinc bacitracin.* Proceed as directed in § 141e.404 (a). Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units per troche that it is represented to contain.

(2) *Neomycin content.* Proceed as directed in § 141e.410 (a) (1) (ii). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.414 Bacitracin-neomycin with vasoconstrictor.

(a) *Potency*—(1) *Bacitracin content.* Proceed as directed in § 141e.405(a). Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Neomycin content.* Proceed as directed in § 141e.410 (b) (1). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.415 Bacitracin-polymyxin troches; zinc bacitracin-polymyxin troches.

(a) *Potency*—(1) *Polymyxin content.* Dissolve five troches in a small amount of 10 percent phosphate buffer, pH 6.0, then add sufficient buffer to give a concentration of 100 units per milliliter and proceed as directed in § 141b.112(b)(1) of this chapter, except § 141b.112(b)(1)(iv). Prepare daily standard curve as directed in § 141a.21(c)(1)(vii) of this chapter, except that: Calculate the amount of sucrose that would be present when the sample is diluted to contain 10 units of polymyxin (labeled potency) per milliliter. Prepare the polymyxin standard curve by adding that amount of sucrose to each concentration of polymyxin used for the curve. Using a solution of the polymyxin working standard in 10 percent potassium phosphate buffer, pH 6.0, prepare volumetrically the following concentrations: 6.4, 8.0, 10.0, 12.5, and 15.6 units per milliliter in 10 percent potassium phosphate buffer, pH 6.0. The 10 units per milliliter concentration is used as the reference point. Use this standard curve to calculate the polymyxin content of the sample.

(2) *Content of bacitracin and zinc bacitracin.* Proceed as directed in § 141e.404(a). Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.416 Bacitracin methylene disalicylate.

(a) *Potency.* Proceed as directed in § 141e.401(a)(1), except in lieu of the directions for preparing the sample in § 141e.401(a)(1)(ii) prepare the sample as follows: Place an accurately weighed sample of approximately 1 gram in a blending jar, add 99 milliliters of an aqueous solution of 2-percent sodium bicarbonate and 1 milliliter of polysorbate 80 and blend for 3 minutes in a high-speed blender. Allow the foam to subside, remove an aliquot of the solution, and dilute to 1 unit per milliliter with 1-percent phosphate buffer.

(b) *Toxicity.* Proceed as directed in § 141d.305 (b) of this chapter, using as the test dose 1 milliliter of a suspension containing 1,000 units of bacitracin activity per mouse.

(c) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(d) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a saturated aqueous solution containing approximately 50 milligrams per milliliter.

§ 141e.417 Powder bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.

(a) *Potency*—(1) *Bacitracin content.* Proceed as directed in § 141e.401(a), except in lieu of the directions for preparing the sample in § 141e.401(a)(1)(ii), prepare the sample as follows: Place an accurately weighed sample of approximately 5 grams in a blending jar, add 40 milliliters of 2.0-percent sodium bicarbonate and swirl until the sample is thoroughly wetted. Allow to stand for 15 minutes with occasional swirling. After standing for 15 minutes, add 30 milliliters of 1-percent potassium phosphate buffer at pH 6.0 and allow to stand for 1 hour, with occasional swirling. Add 30 milliliters of acetone and blend for 2 minutes; allow to stand for 2 minutes and reblend for 2 minutes. Allow to settle for 15 minutes, and filter through filter paper on a Buchner funnel. Remove an aliquot of the filtrate and add sufficient semicarbazide 1.0-percent solution, at pH 6.5–7.0, to inactivate (1 hour at room temperature) the streptomycin contained in the solution. After inactivation, remove an aliquot of this solution and dilute to 1 unit per milliliter with 1.0-percent phosphate buffer. Its potency is satisfactory if it contains not less than 85 percent of the units of bacitracin activity that it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141b.101 of this chapter. Its content of streptomycin is satisfactory if it contains not less than 85 percent of the number of milligrams of streptomycin activity per gram that it is represented to contain.

(b) *Moisture.* Using a 1.0-gram sample, proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.418 Zinc bacitracin (bacitracin zinc salt).

(a) *Potency.* Proceed as directed in § 141e.401(a)(1), except prepare the sample as follows: Suspend an accurately weighed sample of approximately 100 milligrams in 5 milliliters of distilled water. Add 0.5 milliliter of 3 *N* HCl, stir until the sample is dissolved, and transfer to a 100-milliliter volumetric flask and make to volume with distilled water. Dilute an aliquot of this solution to 1.0 unit per milliliter (estimated) with 1-percent phosphate buffer.

(b) *Toxicity.* Administer orally, by means of a cannula or other suitable device, to each of 5 mice within the weight range of 18-25 grams, 0.5 milliliter of a water suspension of the drug containing 4,000 units per milliliter. If no animal dies within 48 hours, the sample is nontoxic. If one or more animals die within

48 hours, repeat the test with 5 unused mice weighing 20 grams (±0.5 gram each); if all animals survive the repeat test, the sample is nontoxic.

(c) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(d) *pH.* Prepare a saturated solution, using approximately 100 milligrams of the sample per milliliter, and proceed as directed in § 141a.5 (b) of this chapter.

(e) *Zinc content*—(1) *Reagents*—(i) *Aqueous working solution.* Dissolve 3.11 grams of the zinc oxide in sufficient 1 *N* HCl and dilute to 250 milliliters with water. Remove a suitable aliquot and dilute with water to obtain 0.1 percent solution.

(ii) *Alkaline buffer solution.* Mix one part 10 *N* ammonium hydroxide and 4.5 parts of 1 *N* ammonium chloride.

(iii) *1 percent phenolphthalein in absolute alcohol.*

(iv) *Ethylenediaminetetraacetic acid sodium working solution.* Dissolve 3.72 grams of ethylenediaminetetraacetic acid sodium in 100 milliliters of water. Remove an aliquot and prepare a 1:25 dilution using water as the diluent.

(v) *1-(1-Hydroxy-2-naphthylazo)-5-nitro-2-naphthol-4-sulfonic acid sodium salt solution.* Prepare daily a 1 percent solution in alkaline buffer.

(2) *Preparation of sample.* Using 2 milliliters of 10 percent acetic acid and 5 milliliters of water, wash an amount of the sample containing approximately 2 milligrams of zinc (usually 40 milligrams to 50 milligrams, into a titration flask. Add 1 drop of phenolphthalein solution. Add 1 *N* NaOH, dropwise, until a heavy precipitate of bacitracin appears and a faint pink color persists.

(3) *Preparation of standard.* Place 2-milliliter aliquots of the 0.1 percent working solution into two titration flasks, respectively, and add one drop of phenolphthalein solution.

(4) *Procedure.* To all titration flasks (standard and sample) add 2 milliliters of alkaline buffer solution, 50 milliliters of water, and 0.1 milliliter of 1-(1-hydroxy-2-naphthylazo)-5-nitro-2-naphthol-4-sulfonic acid sodium salt indicator solution. Titrate with ethylenediaminetetraacetic acid working solution from a burgundy-red color to a blue endpoint.

(5) *Calculation.* From the standards, calculate the milligram equivalent of the ethylenediaminetetraacetic acid solution per milliliter (F).

$$\text{Percent zinc} = \frac{F \times \text{milliliters of ethylenediamine-tetraacetic acid (sample)} \times 100}{\text{Weight of samples in milligrams (on anhydrous basis)}}$$

§ 141e.419 Bacitracin-neomycin-polymyxin troches; zinc bacitracin-neomycin-polymyxin troches.

(a) *Potency*—(1) *Neomycin content.* Proceed as directed in § 141e.410(a)(1)(ii). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams of activity that it is represented to contain.

(2) *Polymyxin content.* Proceed as directed in § 141e.415 (a) (1), except calculate from the quantity of neomycin found (using the method prescribed in subparagraph (1) of this paragraph) the quantity of neomycin that would be present when the sample is diluted to contain 10 units of polymyxin (labeled potency) per milliliter. Prepare the polymyxin standard curve by adding this calculated quantity of neomycin to each concentration of polymyxin used for the curve. Use this standard curve to calculate the polymyxin content of the sample. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(3) *Content of bacitracin or zinc bacitracin.* Proceed as directed in § 141e.404 (a). Its content of bacitracin or zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.420 Bacitracin-tyrothricin-neomycin troches; bacitracin-gramicidin-neomycin troches; zinc bacitracin-tyrothricin-neomycin troches; zinc bacitracin-gramicidin-neomycin troches.

Proceed as directed in § 141e.413 (a) and (b).

§ 141e.421 Bacitracin-neomycin-polymyxin tablets.

(a) *Potency*—(1) *Bacitracin content.* Proceed as directed in § 141e.403(a). Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units per tablet that it is represented to contain.

(2) *Neomycin content.* Proceed as directed in § 141e.410 (a) (1) (ii). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams of activity per tablet that it is represented to contain.

(3) *Polymyxin content.* Proceed as directed in § 141b.112 (a) (1) (ii) of this chapter, except calculate from the quantity of neomycin found (using the method prescribed in subparagraph (2) of this paragraph) the quantity of neomycin that would be present when the sample is diluted to contain 10 units of polymyxin (labeled potency) per milliliter. Prepare the polymyxin standard curve by adding this calculated quantity of neomycin to each concentration of polymyxin used for the curve. Use this standard curve to calculate the polymyxin content of the sample. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units per tablet that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.b) (a) of this chapter.

§ 141e.422 Bacitracin-polymyxin-neomycin ointment.

(a) *Potency*—(1) *Bacitracin content.* Proceed as directed in § 141e.409(a)(1). Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units per gram that it is represented to contain.

(2) *Polymyxin content.* Proceed as directed in § 141e.499 (a) (2), except calculate from the quantity of neomycin found (using the method prescribed in subparagraph (3) of this paragraph) the quantity of neomycin that would be present when the sample is diluted to contain 10 units of polymyxin (labeled potency) per milliliter. Prepare the polymyxin standard curve by adding this calculated quantity of neomycin to each concentration of polymyxin used for the curve. Use this standard curve to calculate the polymyxin content of the sample. Its content of polymyxin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(3) *Neomycin content.* Proceed as directed in § 141e.411 (a) (2). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b) of this chapter.

§ 141e.423 Soluble bacitracin methylene disalicylate.

(a) *Potency.* Proceed as directed in § 141e.401(a)(1), except in lieu of the directions for preparing the sample in § 141e.401(a)(1)(ii), prepare the sample as follows: Place an accurately weighed sample of approximately 1 gram in a blending jar, add 99 milliliters of an aqueous solution of 2 percent sodium bicarbonate and 1 milliliter of polysorbate 80 and blend for 3 minutes in a high-speed blender. Allow the foam to subside. Dilute a suitable aliquot with 1 percent phosphate buffer to a concentration of one unit per milliliter. Its potency is satisfactory if it contains not less than 85 percent of the bacitracin activity per pound that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *pH.* Proceed as directed in § 141a.5 (b) of this chapter, using a solution containing 200 units per milliliter.

§ 141e.424 Bacitracin-neomycin-polymyxin with vasoconstrictor.

(a) *Potency.* Prepare the drug as directed in its labeling and proceed as follows:

(1) *Bacitracin content.* Proceed as directed in § 141e.401 (a). Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(2) *Neomycin content.* Proceed as directed in § 141e.410 (b) (1). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams per milliliter that it is represented to contain.

(3) *Polymyxin B content.* Proceed as directed in § 141b.112 (b) (1) of this chapter, except that:

(i) Calculate from the quantity of neomycin found (using the method prescribed in subparagraph (2) of this paragraph) (the quantity of neomycin that would be present when the sample is diluted to contain 10 units of polymyxin B (labeled potency) per milliliter. Pre-

pare the polymyxin standard curve by adding this calculated quantity of neomycin to each concentration of polymyxin used for the curve. Use this standard curve to calculate the polymyxin content of the sample.

(ii) If the sample contains sodium ethylmercurithiosalicylate, incorporate 0.03 percent thioglycolic acid in the seed layer just before preparing the plates.

(iii) Its content of polymyxin B is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(b) *Moisture (dry components of the drug).* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.425 Bacitracin powder.

(a) *Potency.* Proceed as directed in § 141e.401 (a) (1), except in lieu of the directions for preparing the sample in § 141e.401 (a) (1) (ii), prepare the sample as follows: Place an accurately weighed sample of approximately 1 to 5 grams in a 100-milliliter volumetric flask, dissolve in 1 percent phosphate buffer, and dilute to 100 milliliters with 1 percent phosphate buffer. Dilute a suitable aliquot with 1-percent phosphate buffer to a concentration of 1 unit per milliliter (estimated). Its potency is satisfactory if it contains not less than 85 percent of the number of units of bacitracin per pound that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.426 Tablets bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.

(a) *Potency*—(1) *Bacitracin content.* Use 5 finely powdered tablets and proceed as directed in § 141e.417(a)(1). Its bacitracin activity is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(2) *Streptomycin content.* Proceed as directed in § 141b.109 (a) (1) of this chapter. Its streptomycin activity is satisfactory if it is not less than 85 percent of that which it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(c) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 141e.427 Feed grade bacitracin powder oral veterinary (crude bacitracin powder oral veterinary, unrefined bacitracin powder oral veterinary); feed grade zinc bacitracin powder oral veterinary (crude zinc bacitracin powder oral veterinary, unrefined zinc bacitracin powder oral veterinary).

(a) *Feed grade bacitracin or zinc bacitracin powder oral veterinary*—(1) *Potency.* Proceed as directed in § 141e.425(a), except if it is feed grade zinc bacitracin powder oral veterinary proceed as directed in § 141e.418(a). Their potency is satisfactory if they contain not less than 85 percent of the number of grams of bacitracin or zinc bacitracin per pound that they are represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

(b) *Bacitracin or zinc bacitracin used in making the batch*—(1) *Potency.* Proceed as directed in § 141e.401 (a), except if it is zinc bacitracin proceed as directed in § 141e.418 (a).

(2) *Zinc content (if zinc bacitracin is used).* Proceed as directed in § 141e.418 (e).

(3) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.428 Capsules bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.

(a) *Potency*—(1) *Bacitracin content.* Using a representative number of capsules (usually five) in a blending jar, proceed as directed in § 141e.417(a)(1). Its bacitracin content is satisfactory if it contains not less than 85 percent of that which it is represented to contain.

(2) *Streptomycin content.* Using the contents of a representative number of capsules (usually six), proceed as directed in § 141b.101 (a) to (i), inclusive, of this chapter, and use 0.1 *M* potassium phosphate buffer, pH 8.0, for preparing the sample instead of sterile distilled water as directed in § 141b.101 (e). Its content of streptomycin is satisfactory if it contains not less than 85 percent of that which it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5 (a) of this chapter.

§ 141e.429 Bacitracin-neomycin in oil veterinary.

(a) *Potency*—(1) *Bacitracin content.* Proceed as directed in § 141e.402(a). Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units per milliliter that it is represented to contain.

(2) *Neomycin content.* Prepare the sample as directed in § 141a.8 (a) of this chapter, except in lieu of 1 percent potassium phosphate buffer use 0.10 *M* potassium phosphate buffer (pH 7.8–8.0) and proceed as directed in § 141e.410 (b) (1). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.8 (b) of this chapter.

§ 141e.430 Bacitracin-neomycin-polymyxin powder topical; zinc bacitracin-neomycin-polymyxin powder topical.

(a) *Potency*—(1) *Dry powder*—(i) *Bacitracin content.* Proceed as directed in § 141e.401(a). Its content of bacitracin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(ii) *Zinc bacitracin content.* Proceed as directed in § 141e.418(a). Its content of zinc bacitracin is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(iii) *Neomycin content.* Proceed as directed in § 141e.410(b)(1). Its content of neomycin is satisfactory if it contains not less than 85 percent of the number of milligrams that it is represented to contain.

(iv) *Polymyxin B content.* Proceed as directed in § 141b.112(b)(1) of this chapter. Its content of polymyxin B is satisfactory if it contains not less than 85 percent of the number of units that it is represented to contain.

(2) *Powder packaged with inert gases.* Spray, as directed in the labeling, the entire contents of each container to be tested into a separate 2-liter Erlenmeyer flask, held in a horizontal position. Add 500 milliliters of 0.01 *N* HCl and shake to dissolve the contents. Immediately remove aliquots of this solution and, using the appropriate buffer solutions to make further dilutions, proceed as directed in subparagraph (1) of this paragraph. Calculate the average total amount of each antibiotic expelled from the containers. The total potency is satisfactory if it contains not less than 85 percent of the number of units of zinc bacitracin and polymyxin and not less than 85 percent of the number of milligrams of neomycin that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter, except if it is packaged with inert gases proceed as directed in § 141a.7(c) of this chapter, but in lieu of the direction for preparing the sample in § 141a.7(c)(3), prepare the sample and calculate as follows: Freeze the container by placing in a suitable sharp freezing unit having a temperature not higher than −30° C. After freezing, open the container and remove a representative 10-milliliter aliquot. Place in a Karl Fischer vessel (containing about 15 milliliters of neutralized water in methyl alcohol reagent and 5 milliliters of excess Karl Fischer reagent). Allow to warm to at least 10° C. and titrate to the endpoint.

$$\text{Percent moisture} = \frac{(V_1 - V_2) \times e}{100}.$$

(c) *Microorganism count*—(1) *Culture media.* (i) Prepare nutrient agar as described in § 141a.1 (b) (1) of this chapter, for the test for bacteria.

(ii) For the test for molds and yeasts, use ingredients that conform to the standards prescribed by the U. S. P. or N. F., and prepare Sabouraud's dextrose agar as follows:

Dextrose	40 grams.
Peptone	10 grams.
Agar	15 grams.
Distilled water, q. s.	1,000 milligrams.

pH 5.6 to 5.7 after sterilization.

In lieu of preparing the media from the individual ingredients as described, a dehydrated mixture may be used that, when reconstituted with distilled water, has the same composition as such media. Minor modifications of the individual ingredients specified in this subdivision are permissible if the resulting medium possesses growth-promoting properties at least equal to the medium described.

(2) *Conduct of test for bacteria*—(i) *Dry powder.* Weigh each of five immediate containers. Transfer aseptically an aliquot (approximately 1.0 gram) from each of the weighed containers to each of five sterile flasks containing 200 milliliters of sterile distilled water. Reweigh the containers to determine the

weight of the sample taken. Shake the flasks thoroughly to dissolve the powder. Filter the solution from three of the flasks through each of three sterile membrane bacteriological hydrosol assay filters having a porosity of 0.45μ and a diameter of approximately 47 millimeters. Rinse each filter three times by passing 100 milliliters of sterile distilled water through the filter for each rinsing to remove traces of antibiotic. After washing, place the filter pads (filtering side up) on the surface of each of three agar plates containing nutrient agar as described in subparagraph (1)(i) of this paragraph. Incubate the plates for 5 days at 32° C. Count the number of colonies appearing on each filter pad and calculate therefrom the number of viable microorganisms per gram of powder.

(ii) *Powder packaged with inert gases.* Thoroughly cleanse the valve of each container to be tested with a suitable disinfectant. Into each of five sterile, empty Erlenmeyer flasks stoppered with a cotton plug, spray the entire contents of five separate cans, or the equivalent of 1 gram of powder if the can contains more than this amount, respectively, by removing the plug temporarily and using aseptic technique while spraying. Allow propellant to evaporate, add 250 milliliters of sterile 0.05 percent aqueous sodium thioglycolate, and swirl the flask to dissolve the contents. Then proceed as described in subparagraphs (2)(i) and (3) of this paragraph.

(3) *Conduct of test for molds and yeasts*—(i) *Dry powder.* Proceed as directed in subparagraph (2)(i) of this paragraph (using the remaining two flasks), except use the agar medium as described in subparagraph (1)(ii) of this paragraph, and incubate at 25° C. for 5 days. Count the number of colonies appearing on each filter pad and calculate therefrom the number of viable microorganisms per gram of powder.

(ii) *Powder packaged with inert gases.* Proceed as directed in subparagraph (2)(ii) of this paragraph, except use agar medium as described in subparagraph (1)(ii) of this paragraph, and incubate at 25° C. for 5 days.

(4) *Evaluation of results.* The microorganism count of the sample is satisfactory if the average number of viable microorganisms is not more than 10 per container or per gram.

§ 141e.431 Feed grade manganese bacitracin powder oral veterinary.

(a) Proceed as directed in § 141e.401 (a), except in lieu of subparagraph (1)(ii) prepare the sample as follows:

(1) Place 2 grams of the sample in a 150-milliliter beaker, add 5 milliliters of 10 percent HCl and stir 1 minute. Check pH with test paper. If pH is greater than 2 add more acid until pH 2 is reached. Add 45 milliliters of pyridine-buffer solution (mix 9 volumes pyridine and 31 volumes pH 6.0 buffer) and transfer the mixture to a centrifuge tube. Shake well for 5 minutes then centrifuge for 15 minutes at 2,000 r.p.m. Dilute an aliquot of the clear solution with enough pH 6.0 buffer to obtain an estimated concentration of 0.20 unit per milliliter.

(2) Prepare the following dilutions in 0.1 *M*pH 6 buffer from the stock solution for the standard curve: 0.025, 0.05, 0.1, 0.2, 0.4, and 0.8 unit per milliliter with 0.2 unit per milliliter as the reference concentration. Also add 10 milliliters of agar to each petri dish instead of 21 milliliters.

Its potency is satisfactory if it contains not less than 85 percent of the number of grams of manganese bacitracin per pound that it is represented to contain.

(b) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(c) *Maganese bacitracin used in making the batch*—(1) *Potency.* Proceed as directed in § 141e.418(a).

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *Manganese content*—(i) *Reagents.*

Nitric acid (69.0 percent–71.0 percent) A.C.S.[1]
Sulfuric acid (95.0 percent–98 percent) A.C.S.
Phosphoric acid (85 percent) A.C.S.
Potassium periodate (99.8 percent).

(ii) *Manganese standard solution.* Dissolve in a flask about 300 milligrams of potassium permanganate (A.C.S.) in 100 milliliters of water and boil the solution for about 15 minutes. Stopper the flask, allow it to stand for at least 2 days, and filter through asbestos. Standardize the solution as follows: Weigh accurately about 20 milligrams of sodium oxalate, previously dried at 110° C. to constant weight, and dissolve it in 25 milliliters of water. Add 1 milliliter of sulfuric acid, heat to about 70° C., and slowly add the permanganate solution from a buret, with constant stirring until a pale-pink color is produced that persists for 15 seconds. The temperature at the conclusion of the titration should not be less than 60° C. Calculate the concentration of the manganese in the standard. Store it in a glass-stoppered, amber-colored bottle.

(iii) *Procedure.* Accurately weigh 200 milligrams to 300 milligrams of the sample into a 30-milliliter kjeldahl flask. Add 5 milliliters of nitric acid and 2 milliliters of sulfuric acid, and heat with a full flame, adding nitric acid dropwise as needed to prevent charring of sample until SO_3 fumes appear. Cool, dilute with water, and boil until SO_3 fumes reappear. After cooling, dilute the sample to 50 milliliters. To a 5-milliliter aliquot add 3 milliliters of phosphoric acid, 3 milliliters of sulfuric acid, 0.3 gram of potassium periodate and water to a volume of 75 milliliters. Boil for 5 minutes and continue heating in a boiling water bath for an additional 30 minutes. When cool, dilute the sample to 100 milliliters and determine the permanganate color on a spectrophotometer against a water blank at 525 millimicrons. The amount of manganese that is present can be determined by comparing the absorbance to a standard curve prepared by pipetting 3.0-, 5.0-, 10.0-, and 15.0-milliliter aliquots of the manganese standard solution into separate 100-milliliter volumetric flasks. Add 3.0 milliliters of phosphoric acid and 3.0 milliliters of sulfuric acid to each, and dilute to mark. In a suitable spectrophotometer, determine the absorbance of the solutions at 525 millimicrons, using water as a blank.

[1] American Chemical Society.

PART 146—GENERAL REGULATIONS FOR THE CERTIFICATION OF ANTIBIOTIC AND ANTIBIOTIC-CONTAINING DRUGS

Sec.

146.1 Definitions and interpretations applicable to Parts 146, 146a, 146b, 146c, 146d, 146e, and 147.
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146.24 Penicillin powder for diagnostic use; streptomycin powder for diagnostic use; dihydrostreptomycin powder for diagnostic use; chlortetracycline hydrochloride powder for diagnostic use; tetracycline hydrochloride powder for diagnostic use; chloramphenicol powder for diagnostic use; bacitracin powder for diagnostic use.
146.25 Antibiotic drugs for use in medicated animal feed (antibiotic medicated feed premixes; antibiotic medicated feed concentrates that must be diluted with feed ingredients before they are fed).
146.26 Animal feed containing penicillin; animal feed containing streptomycin; animal feed containing dihydrostreptomycin; animal feed containing chlortetracycline; animal feed containing tetracyline; animal feed containing bacitracin; animal feed containing feed grade zinc bacitracin; animal feed containing bacitracin methylene disalicylate.
146.27 Antibiotics for fish diseases.
146.28 Antibiotics for bull semen.
146.29 Biological drugs that contain antibiotics.
146.30 Exemption for the salts of antibiotic drugs for use in teaching, law enforcement, research, and analysis.

AUTHORITY: §§ 146.1 to 146.29 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

CROSS REFERENCE: For other regulations in this chapter concerning antibiotic and antibiotic-containing drugs, see also §§ 3.15, 3.29, 3.30, 3.501, 3.504, 3.507, and Part 121.

§ 146.1 Definitions and interpretations applicable to Parts 146, 146a, 146b, 146c, 146d, 146e, and 147.

In addition to the definitions and interpretations in this section, the definitions and interpretations contained in section 201 of the Federal Food, Drug, and Cosmetic Act shall be applicable to such terms when used in the regulations covering the certification of antibiotic and antibiotic-containing drugs.

(a) *Definitions of antibiotic substances.* (1) Each of the several antibiotic substances (e. g., penicillin F, penicillin G, penicillin X) produced by the growth of Penicillium notatum or Penicillium chrysogenum, and each of the same substances produced by any other means, is a kind of penicillin.

(2) Each of the several antibiotic substances produced by the growth of Streptomyces griseus, and each of the same substances produced by any other means, is a kind of streptomycin.

(3) Each of the antibiotic substances produced by hydrogenation of streptomycin, and each of the same substances produced by any other means, is a kind of dihydrostreptomycin.

(4) Each of the several antibiotic substances produced by the growth of Streptomyces aurecfaciens, and each of the same substances produced by any other means, is a kind of chlortetracycline.

(5) Each of the several antibiotic substances produced by the hydrogenation of chlortetracycline, and each of the same substances produced by any other means, is a kind of tetracycline.

(6) Each of the several antibiotic substances produced by the growth of Streptomyces venezuelae, and each of the same substances produced by any other means, is a kind of chloramphenicol.

(7) Each of the several antibiotic substances produced by the growth of Bacillus subtilis var. Tracy, and each of the same substances produced by any other means, is a kind of bacitracin.

(b) *Definitions of master standards.* (1) The term "penicillin G master standard" means a specific lot of crystalline sodium penicillin G (sodium penicillin II) that is designated by the Commissioner as the standard of comparison in determining the potency of the penicillin G working standards. The term "penicillin O master standard" means a specific lot of crystalline potassium penicillin O standardized by the penicillin G master standard and which is designated by the Commissioner as the standard of comparison in determining the penicillin O content of the penicillin O working standard. The term "penicillin V master standard" means a specific lot of crystalline penicillin V that is designated by the Commissioner as the standard of comparison in determining the potency of the penicillin V working standard. The term "L-α-phenoxyethyl, penicillin potassium master standard" means a specific lot of L-α-phenoxyethyl, penicillin potassium that is designated by the Commissioner as the standard of comparison in determining the potency of the L-α-phenoxyethyl, penicillin potassium working standard. The term "D-α-phenoxyethyl, penicillin potassium master standard" means a specific lot of D-α-phenoxyethyl, penicillin potassium that is designated by the Commissioner as the standard of comparison in determining the potency of the D-α-phenoxyethyl, penicillin potassium working standard. The term "methicillin sodium master standard" means a specific lot of methicillin sodium that is designated by the Commissioner as the standard of comparison in determining the potency of the methicillin sodium working standard. The term "sodium oxacillin master standard" means a specific lot of sodium oxacillin that is designated by the Commissioner as the standard of comparison in determining the potency of the sodium oxacillin working standard.

(2) The term "streptomycin master standard" means a specific lot of crystalline trihydrochloride calcium chloride salt of streptomycin that is designated by the Commissioner as the standard of comparison in determining the potency of the streptomycin working standard.

(3) The term "dihydrostreptomycin master standard" means a specific lot of crystalline dihydrostreptomycin sulfate that is designated by the Commissioner as the standard of comparison in determining the potency of the dihydrostreptomycin working standard.

(4) The term "chlortetracycline master standard" means a specific lot of crystalline chlortetcycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the chlortetracycline working standard.

(5) The term "demethylchlortetracycline master standard" means a specific lot of crystalline 6-demethylchlortetracycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the 6-demethylchlortetracycline working standard.

(6) The term "tetracycline master standard" means a specific lot of crystalline tetracycline hydrochloride that is designated by the Commissioner as the standard of comparison in determining the potency of the tetracycline working standard.

(7) The term "rolitetracycline master standard" means a specific lot of crystalline rolitetracycline that is designated by the Commissioner as the standard of comparison in determining the potency of the rolitetracycline working standard.

(8) The term "chloramphenicol master standard" means a specific lot of crystalline chloramphenicol that is designated by the Commissioner as the standard of comparison in determining the potency of the chloramphenicol working standard.

(9) The term "bacitracin master standard" means a specific lot of bacitracin that is designated by the Commissioner as the standard of comparison in determining the potency of the bacitracin working standard.

(c) *Definitions of the terms "unit" and "microgram" as applied to antibiotic substances.* (1) (i) The term "unit" applied to penicillin means a penicillin activity contained in 0.6 microgram of the penicillin G master standard, except that the term "unit" applied to penicillin V means a penicillin activity contained in 0.59 microgram of the penicillin V master standard. The term "unit" applied to phenethicillin potassium means a penicillin activity contained in 0.68 microgram of the D- or L-α-phenoxyethyl, penicillin potassium master standard or in 0.61 microgram of the free acid, the latter value being used as a basis of conversion from units to the metric system. The term "penicillin potency" means the number of such units in a specified quantity of a substance.

(ii) The term "unit" applied to bacitracin means a bacitracin activity contained in 23.8 micrograms of the bacitracin master standard after it is dried for 3 hours at 60° C. and a pressure of 5 millimeters or less; the term "bacitracin potency" means the number of such units in a specified quantity of a substance.

(2) (i) The term "microgram" applied to streptomycin means the streptomycin activity (potency) contained in 1.38 micrograms of the streptomycin master standard after it is dried for 4 hours at 56° C. and a pressure of 50 microns or less.

(ii) The term "microgram" applied to dihydrostreptomycin means the dihydrostreptomycin activity (potency) contained in 1.25 micrograms of the dihydrostreptomycin master standard after it is dried for 4 hours at 100° C. and a pressure of 50 microns or less.

(iii) The term "microgram" applied to chlortetracycline means the chlortetracycline activity (potency) contained in 1.0 microgram of the chlortetracycline master standard.

(iv) The term "microgram" applied to 6-demethylchlortetracycline means the 6-demethylchlortetracycline activity (potency) contained in 1.0 microgram of 6-demethylchlortetracycline master standard.

(v) The term "microgram" applied to tetracycline means the tetracycline activity (potency) contained in 1.0 microgram of tetracycline master standard.

(vi) The term "microgram" applied to rolitetracycline means the rolitetracycline activity (potency) contained in 1.0 microgram of the rolitetracycline master standard.

(vii) The term "microgram" applied to chloramphenicol means the chloramphenicol activity (potency) contained in 1.0 microgram of the chloramphenicol master standard.

(viii) The term "microgram" applied to methicillin means the methicillin activity (potency) contained in 1.105 micrograms of the methicillin master standard.

(ix) The term "microgram" applied to oxacillin means the oxacillin activity (potency) contained in 1.0996 micrograms of the sodium oxacillin master standard.

(d) *Definitions of working standards.* (1) (i) The term "penicillin G working standard" means a specific lot of a homogeneous preparation of one or more salts of penicillin.

(ii) The term "penicillin O working standard" means a specific lot of a homo-

geneous preparation of potassium penicillin O.

(iii) The term "penicillin V working standard" means a specific lot of a homogeneous preparation of penicillin.

(iv) The term "L-α-phenoxyethyl, penicillin potassium working standard" means a specific lot of a homogeneous preparation of L-α-phenoxyethyl, penicillin potassium. The term "D-α-phenoxyethyl, penicillin potassium working standard" means a specific lot of a homogeneous preparation of D-α-phenoxyethyl penicillin potassium.

(v) The term "methicillin working standard" means a specific lot of a homogeneous preparation of methicillin.

(vi) The term "sodium oxacillin working standard" means a specific lot of a homogeneous preparation of sodium oxacillin.

(2) [Reserved]

(3) [Reserved]

(4) The term "streptomycin working standard" means a specific lot of a homogeneous preparation of one or more streptomycin salts.

(5) The term "dihydrostreptomycin working standard" means a specific lot of a homogeneous preparation of one or more dihydrostreptomycin salts.

(6) The term "chlortetracycline working standard" means a specific lot of a homogeneous preparation of one or more chlortetracycline salts.

(7) The term "demethylchlortetracycline working standard" means a specific lot of a homogeneous preparation of one or more 6-demethylchlortetracycline salts.

(8) The term "tetracycline working standard" means a specific lot of a homogeneous preparation of one or more tetracycline salts.

(9) The term "rolitetracycline working standard" means a specific lot of a homogeneous preparation of one or more rolitetracycline salts.

(10) The term "chloramphenicol working standard" means a specific lot of a homogeneous preparation of one or more chloramphenicols.

(11) The term "bacitracin working standard" means a specific lot of a homogeneous preparation of one or more bacitracins.

The potency or purity of each preparation has been determined by comparison with its master standard, and each has been designated by the Commissioner as working standards for use in determining the potency or purity of antibiotic substances subject to the regulations in this chapter.

(e) *Miscellaneous definitions.* (1) The term "batch" means a specific homogeneous quantity of a drug.

(2) The term "batch mark" means an identifying mark or other identifying device assigned to a batch by the manufacturer or packer thereof.

(3) The term "Commissioner" means the Commissioner of Food and Drugs and any other officer of the Food and Drug Administration whom he may designate to act in his behalf for the purpose of the regulations for the certification of antibiotic and antibiotic-containing drugs.

(4) The term "U. S. P." means the official Pharmacopeia of the United States, including supplements thereto. The term "N. F." means the official National Formulary, including supplements thereto.

(5) The term "manufacture" does not include the use of a drug as an ingredient in compounding any prescription issued by a practitioner licensed by law to administer such drug.

(f) All statements, samples, and other information and materials submitted in connection with a request for certification shall be considered to be part of such request.

(g) Except as specifically provided by regulations in Parts 146, 146a, 146b, 146c, 146d, 146e, and 147 of this chapter, no provision of any regulation in such parts shall be construed as exempting any drug from any applicable provision of the act or any regulation thereunder.

(h) The regulations in Parts 141a, 141b, 141c, 141d, 141e, and 147 of this chapter, prescribing tests and methods of assay, shall not be construed as preventing the Commissioner from using any other test or method of assay in his investigations to determine whether or not:

(1) A request for certification contains any untrue statement of a material fact; or

(2) A certification has been obtained through fraud, or through misrepresentation or concealment of a material fact.

(i) Wherever the potency of an antibiotic drug included in the regulations in this chapter is expressed in terms of weight, such potency shall be equivalent to that contained in the same weight of the master standard of the drug.

(j) At the option of the person having control of records required to be kept by any section in this part, photostatic or other permanent reproductions may be substituted for such records after the first 2 years of the holding period.

(k) [Reserved.]

(l) *Penicillin and penicillin-containing drugs intended for treatment or prevention of mastitis in dairy animals by intramammary infusion; dosage limitation.* Whenever the labeling of a penicillin or penicillin-containing drug included in the regulations in this chapter suggests or recommends its use in the prevention or treatment of mastitis in dairy animals by intramammary infusion, the penicillin content of each single dose shall not exceed 100,000 units when used as directed in such labeling.

(m) The expiration date prescribed for a drug by the regulations in this chapter may be omitted from the label of the immediate container if such container contains a single dose and it is packaged in an individual wrapper or container that bears the date prescribed.

§ 146.2 Requests for working standards and certification; information and samples required.

(a) A request for certification of a batch shall be addressed to the Commissioner and shall be in a form specified by him. A request from a foreign manufacturer shall be signed by such manufacturer and by an agent of such manufacturer who resides in the United States.

(b) The initial request for certification of a batch of any drug submitted by any person shall be preceded or accompanied by a full statement of the facilities and controls used to maintain the identity, strength, quality, and purity of each batch, including a description of (1) the methods and processes used in the manufacture of the drug; (2) the tests and assays of the drug made during the manufacture of the batch and after it is packaged; and (3) the laboratory facilities used in such controls. Such initial request shall also be preceded or accompanied by the key of the batch marks used by such person and by specimens of all labeling (including specimens of all brochures and other printed matter except readily available medical publications, referred to in such labeling) to be used for such drug. When any change is made in any such facility or control, or in any such key or labeling, such person shall promptly submit to the Commissioner a full statement of such change or, in the case of changed labeling, specimens showing all such changes.

(c) Each sample submitted pursuant to the regulations in this chapter shall be addressed to the Commissioner. Its package shall be clearly identified as to its contents and shall bear the name and post-office address of the person submitting it.

(d) In addition to the information and samples specifically required to be submitted to the Commissioner by the regulations in this chapter, the person who requests certification of a batch shall submit such further information and samples as the Commissioner may require for the purpose of investigations to determine whether or not such batch complies with the requirements of § 146.3 for the issuance of a certificate.

(e) Upon the request of any person, stating reasonable grounds therefor, the Commissioner shall furnish such person with a portion of the working standards.

§ 146.3 Certification.

(a) If it appears to the Commissioner, after such investigation as he considers necessary, that:

(1) The information (including results of tests and assays) and samples required by or pursuant to the regulations in this chapter have been submitted, and the request for certification contains no untrue statement of a material fact; and

(2) The batch complies with the regulations in this chapter and conforms to the applicable standards of identity, strength, quality, and purity prescribed by the regulations in this chapter;

the Commissioner shall certify that such batch is safe and efficacious for use, subject to such conditions on the effectiveness of certificates as are prescribed by § 146.4; and shall issue to the person who requested it a certificate to that effect.

(b) If the Commissioner determines, after such investigation as he considers to be necessary, that the information submitted pursuant to the regulations in this chapter, or the batch covered by such request, does not comply with the requirements set forth in paragraph (a) of this section for the issuance of a cer-

tificate, the Commissioner shall refuse to certify such batch and shall give notice thereof to the person who requested certification, stating his reasons for refusal.

(c) Compliance of a drug with the standards of identity, strength, quality, and purity prescribed by regulations in this chapter shall be determined by the tests and methods of assay prescribed for such drug by regulations in Parts 141a to 141e and § 147.2 of this chapter.

§ 146.4 Conditions on the effectiveness of certificates.

(a) A certificate shall not become effective:

(1) If it is obtained through fraud or through misrepresentation or concealment of a material fact;

(2) With respect to any package unless it complies with the packaging requirements, if any, prescribed by the regulations in this chapter which were in effect on the date of the certificate;

(3) With respect to any package unless its label and labeling bear all words, statements, and other information required by the regulations in this chapter; or

(4) With respect to any package of a certifiable antibiotic drug subject to the regulations in this chapter, when it is included in a packaged combination with another drug, unless such other drug complies with the requirements of the regulations in this chapter.

(b) A certificate shall cease to be effective:

(1) With respect to any immediate container after the expiration date, if any, prescribed by the regulations in this chapter;

(2) With respect to any immediate container when it or its seal (if the regulations in this chapter require it to be sealed) is broken, or when its label or labeling is altered, mutilated, destroyed, obliterated, or removed in whole or in part, or ceases to conform to any labeling requirement prescribed by the regulations in this chapter, except that:

(i) If the drug in such container is repacked or used as an ingredient in the manufacture of another drug, and certification of the batch thus made is requested, such certificate shall continue to be effective for a reasonable time to permit certification or destruction of such batch;

(ii) If the drug is in a container packaged for dispensing and is used in compounding a prescription issued by a practitioner licensed by law to administer such drug, such certificate shall continue to be effective for a reasonable time to permit the delivery of the drug compounded on such prescription; or

(iii) If its label or labeling is removed in whole or in part for the purpose of relabeling and supplemental certification of the relabeled drug is requested, as provided by § 146.18.

(3) With respect to any immediate container of penicillin when it is included in the packaged combination penicillin with aluminum hydroxide gel or penicillin with a vasoconstrictor, or to any immediate container of bacitracin when it is included in the packaged combination bacitracin with a vasoconstrictor, except that when certification of the batch so included is requested, such certificate shall continue to be effective for a reasonable time to permit certification of such batch which is part of such combination;

(4) With respect to any package when the drug therein fails to meet the standards of identity, strength, quality, and purity which were in effect on the date of the certificate; except that those minor changes which occur before the expiration date and which are normal and unavoidable in good storage and distribution practice shall be disregarded.

(5) With respect to any package of a certifiable antibiotic drug subject to the regulations in this chapter, included in a packaged combination with another drug, when such other drug fails to meet the requirements of the regulations in this chapter; or

(6) With respect to any immediate container, if such regulations require its labeling to bear a caution against dispensing otherwise than on prescription, at the beginning of the act of dispensing or offering to dispense it otherwise than:

(i) By a practitioner licensed by law to administer such drug; or

(ii) On his prescription issued in his professional practice.

§ 146.5 Records of distribution.

(a) The person who requested certification shall keep complete records showing each shipment and other delivery (including exports) of each certified batch or part thereof by such person or by any person subject to his control. Such records shall show the date and quantity of each such shipment or delivery and the name and post-office address of the person to whom such shipment or delivery was made, and shall be kept for not less than three years after such date.

(b) Upon the request of any officer or employee of the Food and Drug Administration, or of any other officer or employee of the United States acting on behalf of the Secretary, the person to whom a certificate is issued shall at all reasonable hours make such records available to any such officer or employee and shall accord to him full opportunity to make inventory of stocks of such batch on hand and otherwise to check the correctness of such records.

§ 146.6 Authority to refuse certification service.

When the Secretary finds, after giving notice and opportunity for hearing, that a person has:

(a) Obtained or attempted to obtain a certificate through fraud, or through misrepresentation or concealment of a material fact;

(b) Falsified the records required to be kept by § 146.5; or

(c) Failed to keep such records or to make them available, or to accord full opportunity to make an inventory of stocks on hand or otherwise to check the correctness of such records, as required by § 146.5, and such failure may materially impair the certification service;

the Secretary will immediately suspend service to such person under the regulations in this chapter and will continue such suspension unless and until such person shows adequate cause why such service should be resumed.

§ 146.7 New antibiotic and antibiotic-containing products.

Any request that the Secretary provide for the certification of batches of a drug for which no provision for certification is made in the existing regulations in this chapter shall be in a form specified by the Commissioner and shall be accompanied by:

(a) A statement of the conditions for which the person who makes such request intends such drug to be used, and adequate directions for use in each such condition;

(b) Full reports of investigations which have been made to show whether or not such drug is safe and efficacious for use in such conditions;

(c) A full list of the articles used as components of such drug;

(d) A full statement of the composition of such drug;

(e) A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(f) A full description of, or references to publications containing practical and accurate tests and methods of assay to determine the identity, strength, quality, and purity of such drug;

(g) Such samples of such drug and of the articles used as components thereof as the Commissioner may require; and

(h) Specimens of all labeling (including all brochures and other printed matter, except readily available medical publications, referred to in such labeling) proposed to be used for such drug.

§ 146.8 Fees.

(a) Fees for the services rendered under the regulations in this chapter shall be such as are necessary to provide, equip, and maintain an adequate certification service.

(b) The fee for such services with respect to each batch of a drug, certification of which is provided by the regulations in this chapter, including those published hereafter, is the fee prescribed in the section relating specifically to such drug plus an additional 30 percent of whatever that fee may be, except that in the case of a supplemental request submitted pursuant to the provisions of § 146.18, the fee shall be $3.00.

(c) When the Commissioner considers it necessary to make investigations of a new product containing a certifiable antibiotic drug on which a request has been submitted in accordance with § 146.7, the fee for such service shall be the cost thereof. In such case the request shall be followed by an advance deposit in such amount as the Commissioner specifies, and thereafter such additional advance deposits shall be made as the Commissioner estimates may be necessary to prevent arrears in the payment of such fee.

(d) A person requiring continuing certification services may maintain an advance deposit of the estimated cost of

such services for a two-month period. Such deposit shall be debited with fees for services rendered, but shall not be debited for any fee the amount of which is not definitely specified in the regulations in this chapter unless the depositor has previously requested the performance of the services to be covered by such fee. A monthly statement for each such advance deposit shall be rendered.

(e) The unearned portion of any advance deposit shall be refunded to the depositor upon his application.

(f) Whenever in the judgment of the Commissioner the ratio between fees collected (which are based upon experience and the best estimate of costs and the best estimate of earnings) and the costs of providing the service during an elapsed period of time, in the light of all circumstances and contingencies, warrants a refund from the fund collected during such period, he shall make ratable refunds to those persons to whom the services were rendered and charged, except for those services described under § 146.18 and § 146.26.

(g) All deposits and fees required by the regulations in this chapter shall be paid by money order, bank draft, or certified check drawn to the order of the Food and Drug Administration, collectible at par at Washington, D.C. All such deposits and fees shall be forwarded to the Food and Drug Administration, Department of Health, Education, and Welfare, Washington 25, D.C., whereupon after making appropriate records thereof they will be transmitted to the Chief Disbursing Officer, Division of Disbursement, Treasurer of the United States, for deposit to the special account "Salaries and Expenses, Certification, Inspection, and Other Services, Food and Drug Administration."

§ 146.9 Antibiotics for agricultural use.

An article that contains one or more of the antibiotic substances subject to certification under section 507 of the act and intended solely for application to plants for the control of plant diseases caused by microorganisms and conspicuously so labeled is not subject to the requirements of sections 502(l) and 507 of the Federal Food, Drug, and Cosmetic Act, if it contains one or more suitable denaturants that make it unfit for drug use; but in no case shall it be exempt from the requirements of sections 502(l) and 507 of the act if it is represented or intended to be administered to man or other animals for the cure, mitigation, treatment, or prevention of disease or as an animal feed supplement.

§ 146.10 Antibiotics for export.

Drugs containing penicillin, streptomycin, dihydrostreptomycin, chlortetracycline, tetracycline, chloramphenicol, or bacitracin intended for export will be certified notwithstanding failure to meet the labeling requirements of the applicable monographs if the labeling used for such drugs complies with the following conditions:

(a) It has been approved before use by the government authorities of the country to which the drugs are intended for export; and

(b) Such labeling represents that such drugs are for use only in those conditions for which they are certified for domestic distribution.

§ 146.11 Assay requirements for antibiotic drugs exempted from certification.

(a) On December 3, 1953, the regulations for the certification of antibiotic and antibiotic-containing drugs were amended to exempt penicillin troches and bacitracin ointment from the certification requirements under sections 502 (l) and 507 of the act, provided the drugs comply with certain prescribed standards. Since that time a number of veterinary preparations that contain the antibiotic drugs subject to the regulations in this chapter have also been exempted, under certain conditions. One of these conditions is that the label of each package shall bear an expiration date which is determined from the date "during which the batch was last assayed and released by the manufacturer."

(b) It has come to the attention of the Food and Drug Administration that a number of manufacturers and/or repackers do not test these drugs to determine if they comply with the standards prescribed for them by the regulations. It is the position of the Food and Drug Administration that if each batch of such drugs is not tested by the manufacturer or his agent to determine whether it complies with the standards of identity, strength, quality, and purity prescribed for it, the batch is not exempt from certification and it may be deemed to be misbranded under section 502 (l) of the act when in interstate commerce.

(Interprets or applies sec. 502, 52 Stat. 1050, as amended; 21 U. S. C. 352)

§ 146.12 Antibiotic drugs exempted from certification requirements under section 507(c) of the Federal Food, Drug, and Cosmetic Act.

(a) Section 507(a) of the Federal Food, Drug, and Cosmetic Act directs the Secretary of Health, Education, and Welfare to promulgate regulations that shall provide for the certification of batches of drugs composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, or bactitracin, or any derivative thereof. Subsection (c) of that section of the act requires the Secretary to exempt any drug or class of drugs from the certification requirements when in his judgment such requirements are not necessary to insure their safety and efficacy of use. Under the provisions of that subsection, a variety of antibiotic drugs have been exempted from predistribution testing and certification requirements, including those intended for human, veterinary, and miscellaneous uses.

(b) From time to time the Food and Drug Administration has received requests from interested persons for information concerning the kinds of antibiotic preparations that have been exempted from certification. Since there may be others who are interested in having this information, the names of the exempt drugs are listed in subparagraphs (1), (2), and (3) of this paragraph. All the preparations listed, with the exception of crystalline penicillin G sodium and crystalline penicillin G potassium, are exempt only if they comply with certain requirements prescribed for them by the exempting regulations; furthermore, if crystalline penicillin G sodium or crystalline penicillin G potassium is used in the manufacture of another drug, it must comply with the standards of identity, strength, quality, and purity specified for its use in the manufacture of such drug.

(1) The following antibiotic drugs intended for human use have been exempted from certification:

Crystalline penicillin G sodium.
Crystalline penicillin G potassium.
Bacitracin ointment.
Buffered crystalline penicillin G (sodium) for parenteral use.
Buffered crystalline penicillin G (potassium) for parenteral use.
Penicillin troches.

(2) The following antibiotic drugs intended for veterinary use have been exempted from certification:

Buffered crystalline penicillin G (sodium) for parenteral use.
Buffered crystalline penicillin G (potassium) for parenteral use.
Penicillin tablets.
Buffered penicillin powder.
Benzathine penicillin G oral suspension.
Penicillin-streptomycin tablets.
Penicillin-dihydrostreptomycin tablets.
Penicillin-streptomycin powder with or without added vitamin substances, intended for oral use.
Penicillin-dihydrostreptomycin powder with or without added vitamin substances, intended for oral use.
Streptomycin for inhalation therapy.
Dihydrostreptomycin for inhalation therapy.
Streptomycin sulfate powder oral veterinary.
Dihydrostreptomycin powder oral veterinary.
Streptomycin hydrochloride (or sulfate) solution oral veterinary.
Streptomycin-dihydrostreptomycin for inhalation therapy.
Streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary.
Chlortetracycline powder, tetracycline powder, and tetracycline hydrochloride powder for oral use.
Chlortetracycline hydrochloride tablets.
Crude chlortetracycline oral veterinary.
Chlortetracycline hydrochloride powder topical and tetracycline hydrochloride powder topical.
Soluble bacitracin methylene disalicylate.
Bacitracin powder for oral use.
Feed grade bacitracin and feed grade zinc bacitracin oral veterinary.
Antibiotic-medicated animal feeds that are intended for use in promoting the growth rate of certain animals.
Antibiotic-medicated animal feeds that also contain prescribed amounts of one or more active drug ingredients and are intended for use in promoting the growth rate of certain animals.
Antibiotic-medicated animal feeds that contain prescribed amounts of specific antibiotics and are intended for use in the prevention or treatment of specific diseases of certain animals.
Antibiotic-medicated animal feeds that also contain prescribed amounts of one or more other active drug ingredients and are intended for use in promoting the growth rate (because of the antibiotics) and for the

prevention or treatment of specific diseases (because of the other active drug ingredients) of certain animals.

Antibiotic-medicated animal feeds that contain prescribed amounts of antibiotics and also prescribed amounts of one or more other active drug ingredients and are intended for use in the prevention or treatment of specific diseases of animals which are amenable to the combination drug.

(3) The following antibiotic drugs for miscellaneous uses have been exempted from certification:

Antibiotics for agricultural use.
Antibiotics for diagnostic use.
Antibiotics for fish diseases.
Antibiotics for use as preservatives of bull semen.
Antibiotics for use as preservatives of biological drugs.
Antibiotics for use in teaching, law enforcement, research, and analysis.

(c) It is reasonable to assume that other antibiotic preparations will be exempted from the certification requirements. However, because of their unique importance in the treatment of serious infections suffered by large segments of the population, it would not be in the best interests of the public health to exempt any antibiotic drug from certification until experience has proved that all manufacturers can consistently produce batches of the drug that are safe and efficacious for use. Exceptions to this policy will be considered when it has been determined that a preparation is no longer of sufficient importance to the public health to require the certification type of control, or when the preparation is intended for use solely in a manner that will not affect the public health.

§ 146.13 Manganese bacitracin medicated animal feed.

Animal feed containing feed grade manganese bacitracin powder oral veterinary, with or without added suitable vitamin substances, shall be exempt from the requirements of section 502(*l*) and 507 of the act, under the following conditions:

(a) It is intended for use solely as an aid in stimulating the growth and improving the feed efficiency of chickens, turkeys, and swine.

(b) It contains, per ton of feed, the equivalent of the following quantities of the bacitracin master standard as feed grade manganese bacitracin powder oral veterinary:

(1) For chickens and turkeys: Not less than 4 grams and not more than 50 grams; or it may contain a combination of manganese bacitracin and penicillin, in which case it shall contain not less than 3 grams of manganese bacitracin and not less than 0.6 gram of penicillin, but not more than 50 grams of the combination drug.

(2) For swine: Not less than 10 grams and not more than 50 grams.

§ 146.14 Antibiotic and antibiotic-containing drugs intended for use in milk-producing animals; labeling.

Whenever the labeling of an antibiotic drug included in the regulations in this chapter suggests or recommends its use in milk-producing animals, the label of such drugs shall bear either the statement "Warning: Not for use in animals producing milk, since this use will result in contamination of the milk" or the statement "Warning: Milk taken from treated animals within — hours after the latest treatment must not be used for food", and the blank has been filled in with the figure, which shall not be greater than 96, that the Commissioner has authorized the manufacturer of the drug to use. The Commissioner shall determine what such figure shall be from information submitted by the manufacturer and which the Commissioner considers is adequate to prove that period of time after the latest treatment that the milk from treated animals will contain no residues from use of the preparation. If the use of the antibiotic drug as recommended does not result in its appearance in the milk neither of the above warning statements is required.

§ 146.18 Exemptions for labeling.

(a) Except as provided by paragraphs (c) and (d) of this section, a shipment or other delivery of a drug which is to be labeled at an establishment located elsewhere than at the place of manufacture shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment, from the requirements of section 502 (l) of the act if the labeling of each shipping container bears the batch mark of the drug, the number of units per package, the expiration date, and if the person who introduced such shipment or delivery into interstate commerce holds a permit from the Commissioner authorizing shipment for labeling in such establishment.

(b) (1) An application for such a permit shall be in a form specified by the Commissioner, and shall give the name and location of the establishment in which such labeling is to be done.

(2) In case the applicant is the operator of such establishment, the application shall include a written agreement signed by him that he will request certification of each batch from which any shipment or delivery is made to such establishment unless it is exempt under section 801 (d) of the act or § 146.23; that he will not remove any of such drug from such establishment unless it complies with section 502 (l) of the act or is so exempt, or if certification is refused, unless it is returned within a reasonable time to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured; that he will keep complete records showing the date, quantity, and batch mark of each such shipment and delivery and the disposition thereof; that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such disposition; and that he will accord full opportunity to such officer or employee to make inventories of stocks on hand and otherwise check the correctness of such records.

(3) In case the applicant is not the operator of such establishment such application shall include or be accompanied by:

(i) A written agreement signed by the applicant that he will request certification of each batch from which any shipment or delivery is made to such establishment unless it is exempt under section 801 (d) of the act or § 146.23; that he will keep complete records showing the date, quantity, and batch mark of each such shipment and delivery; and that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such shipment or delivery; and

(ii) A written agreement signed by the operator of such establishment that he will submit a request, supplemental to that of the applicant, for the certification of each batch or portion thereof comprised in any such shipment or delivery received by him unless it is exempt under section 801 (d) of the act or § 146.23; that he will specify in his request the number of packages of each size in such shipment or delivery, the date of delivery, the batch mark thereof, and the batch mark he will use therefor; that the batch marks to be used (if different from those of the applicant) will be only those of which the key is specified in this agreement that the expiration date used for the batch will be only that assigned to the manufacturer by certification; that the labeling to be used for such packages will be only that of which specimens are attached to this agreement (including specimens of all brochures and other printed matter, except readily available medical publications, referred to in such labeling); that when any change is made in such key or labeling he will promptly submit to the Commissioner a full statement of such change or, in the case of changed labeling, specimens showing all such changes; that he will not remove any of such drug from such establishment unless it complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or § 146.23 or, if certification is refused, unless it is returned within a reasonable time to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured; that he will keep complete records of the disposition of each such shipment and delivery; that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such disposition; and that he will accord full opportunity to such officer or employee to make inventories of stocks on hand and otherwise check the correctness of such records.

(4) When the Commissioner finds, after giving notice and opportunity for hearing, that such application contains any untrue statement of a material fact or that any provision of any such agreement has been violated he may revoke such permit.

(c) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is the operator of such establishment, shall become void at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof, before or after labeling, from such estab-

lishment unless such batch complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or § 146.23 or, if certification is refused, unless such shipment or delivery is returned within a reasonable time to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured.

(d) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is not the operator of such establishment, shall expire at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof, before or after labeling, from such establishment unless such batch complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or § 146.23 or, if certification is refused, unless such shipment or delivery, within a reasonable time, is destroyed or returned to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured.

§ 146.19 Exemptions for storage.

(a) Except as provided by paragraphs (c) and (d) of this section, a shipment or other delivery of a drug which is to be stored at a warehouse located elsewhere than at the place of manufacture shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such warehouse, from the requirements of section 502 (l) of the act if the labeling of each shipping container bears the batch mark of the drug, and if the person who introduced such shipment or delivery into interstate commerce holds a permit from the Commissioner authorizing shipment for storage in such warehouse.

(b) An application for such a permit shall be in a form specified by the Commissioner, and shall give the name and location of the warehouse in which such drug is to be stored. Such application shall be accompanied by:

(1) A written agreement signed by the applicant that he will request certification of each batch thereof unless it is exempt under section 801 (d) of the act or §§ 146.18, 146.21, or 146.22, that he will not remove any of such drug from such warehouse unless it complies with section 502 (l) of the act or is so exempt or, if certification is refused unless it is returned within a reasonable time to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured; that he will keep complete records showing the date, quantity, and batch mark of each shipment and other delivery of any such drug to such warehouse, and that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such shipment or delivery; and

(2) A written statement signed by the operator of such warehouse showing that he has adequate facilities for such storage; such statement shall contain an agreement that he will hold each shipment or other delivery of such drug intact, under such conditions as will not cause failure of the drug to comply with the requirements for certification, that he will keep complete records showing the date of receipt by him and the quantity and batch mark of each such shipment and delivery and the disposition thereof, that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such disposition, and that he will accord full opportunity to such officer or employee to make inventories of stocks on hand and otherwise check the correctness of such records.

If the applicant keeps complete records showing the date, quantity, and batch mark of each shipment and other delivery of any such drug from such warehouse and the name and post-office address of the person to whom such shipment or delivery was made, the agreement to keep records of such disposals, to make such records available, and to afford opportunity for checking their correctness may be included in the applicant's agreement and omitted from that of the operator. When the Commissioner finds, after giving notice and opportunity for hearing, that such application contains any untrue statement of a material fact or that any provision of any such agreement has been violated he may revoke such permit.

(c) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is the operator of such warehouse, shall become void at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof from such warehouse unless such batch complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or §§ 146.18, 146.21, or 146.22, or, if certification is refused, unless such shipment or delivery is returned within a reasonable time to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured.

(d) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is not the operator of such warehouse, shall expire at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof from such warehouse unless such batch complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or §§ 146.18, 146.21, or 146.22, or, if certification is refused, unless such shipment or delivery, within a reasonable time, is destroyed, or returned to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured.

§ 146.20 Exemptions for processing.

(a) Except as provided by paragraphs (c) and (d) of this section, a shipment or other delivery of any certifiable antibiotic drug subject to the regulations in this chapter in concentrated aqueous solution which is to be processed at an establishment located elsewhere than at the place of manufacture shall be exempt during the time of introduction into and movement in interstate commerce and the time of holding in such establishment from the requirements of section 502 (l) of the act, if the person who introduced such shipment or delivery into interstate commerce holds a permit from the Commissioner authorizing shipment for processing in such establishment, and each package of such solution bears the batch mark of the drug.

(b) An application for such a permit shall be in a form specified by the Commissioner and shall give the name and location of the establishment in which such processing is to be done. Such application shall be accompanied by:

(1) A written agreement signed by the applicant that he will keep complete records showing the date, quantity, potency, and batch mark of each shipment and other delivery of any such solution to such establishment, and that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such shipment or delivery;

(2) A written statement signed by the operator of such establishment showing that he has adequate facilities for such processing; such statement shall contain an agreement that he will keep complete records showing the date of receipt by him and the quantity and batch mark of each such shipment and delivery and the disposition thereof, that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after date of such disposition, and that he will accord full opportunity to such officer or employee to make inventories of stocks on hand and otherwise check the correctness of such records; and

(3) A written agreement signed by the person who will own the drug after the processing is completed that he will request certification of each batch thereof unless it is exempt under section 801 (d) of the act or §§ 146.18, 146.19, 146.21, 146.22, or 146.23, and that he will not remove any of such drug from such establishment unless it complies with section 502 (l) of the act or is so exempt. When the Commissioner finds, after giving notice and opportunity for hearing, that such application contains any untrue statement of a material fact or that any provision of any such agreement has been violated he may revoke such permit.

(c) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is the operator of such establishment, shall become void at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof, before or after processing, from such establishment unless the batch made from such shipment or delivery complies with section 502 (l) of the act or is exempt under

section 801 (d) of the act or §§ 146.18, 146.19, 146.21, 146.22, or 146.23 or, if certification is refused, unless such shipment or delivery is reprocessed and certified or destroyed within a reasonable time.

(d) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is not the operator of such establishment, shall expire at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof, before or after processing, from such establishment unless the batch made from such shipment or delivery complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or §§ 146.18, 146.19, 146.21, 146.22, or 146.23, or, if certification has been refused, unless such shipment or delivery is reprocessed and certified or destroyed within a reasonable time.

§ 146.21 Exemptions for repacking.

(a) Except as provided by paragraphs (c) and (d) of this section, a shipment or other delivery of a drug which is to be repacked at an establishment located elsewhere than at the place of manufacture shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment from the requirements of section 502 (l) of the act if the labeling of each container bears the batch mark of the drug and the number of units per package, and if the person who introduces such shipment or delivery into interstate commerce holds a permit from the Commissioner authorizing shipment for repacking in such establishment.

(b) An application for such a permit shall be in a form specified by the Commissioner, and shall give the name and location of the establishment in which such repacking is to be done. Such application shall be accompanied by:

(1) A written agreement signed by the applicant that he will keep complete records showing the date, quantity, and batch mark of each shipment and other delivery of any such drug to such establishment, and that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of each shipment or delivery;

(2) A written statement signed by the operator of such establishment showing that he has adequate facilities for such repacking; such statement shall contain an agreement that he will keep complete records showing the date of receipt by him and the quantity and batch mark of each such shipment and delivery and the disposition thereof, that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such disposition, and that he will accord full opportunity to such officer or employee to make inventories of stocks on hand and otherwise check the correctness of such records; and

(3) A written agreement signed by the person who will own the drug after the repacking is completed that he will request certification of each batch thereof unless it is exempt under section 801 (d) of the act or §§ 146.18, 146.19, or 146.23, and that he will not remove any of such drug from such establishment unless it complies with section 502 (l) of the act or is so exempt or is returned to him for labeling or, if certification is refused, unless it is returned within a reasonable time to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured.

When the Commissioner finds, after giving notice and opportunity for hearing, that such application contains any untrue statement of a material fact or that any provision of any such agreement has been violated he may revoke such permit.

(c) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is the operator of such establishment, shall become void at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof, before or after repacking, from such establishment unless such batch complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or §§ 146.18, 146.19, or 146.23 or is returned to such person for labeling or, if certification is refused, unless such shipment or delivery is returned within a reasonable time to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured.

(d) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is not the operator of such establishment, shall expire at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof, before or after repacking, from such establishment unless such batch complies with section 502 (l) of the act or is exempt under section 801 (d) of the act or §§ 146.18, 146.19, or 146.23 or is returned to such person for labeling or, if certification is refused, unless such shipment or delivery, within a reasonable time, is destroyed or returned to permit reprocessing and certification, destruction, or such exemption at the establishment where it was manufactured.

§ 146.22 Exemptions for manufacturing use.

(a) Except as provided by paragraphs (c) and (d) of this section, a shipment or other delivery of any certifiable antibiotic drug subject to the regulations in Parts 146a, 146b, 146c, 146d, and 146e and § 147.2 of this chapter which is packed in containers of not less than 10,000,000 units of penicillin or 10 grams of streptomycin, dihydrostreptomycin, chlortetracycline, tetracycline, chloramphenicol, or bacitracin, each shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in the establishment where it is so used, from the requirements of section 502 (l) of the act, if it conforms to the standards prescribed therefor by the section of the regulations in this chapter which is specifically applicable to such other drug, if the label of each container bears the batch mark of the drug, the number of units or grams per package, and the date on which the latest assay of the drug was completed, and if the person who introduced each shipment or delivery into interstate commerce holds a permit from the Commissioner authorizing shipment for manufacturing use in such establishment.

(b) An application for such a permit shall be in a form specified by the Commissioner, shall give the name and location of the establishment in which such drug is to be used and shall be accompanied by:

(1) A written agreement signed by the applicant that he will keep complete records showing the date, quantity, and batch mark of each shipment and other delivery of any such drug to such establishment, and that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such shipments or delivery;

(2) A written statement signed by the operator of such establishment showing that he has adequate facilities for the manufacture of such other drug; such statement shall contain an agreement that he will keep complete records showing the date of receipt by him and the quantity and batch mark of each such shipment and delivery and the disposition thereof and showing the quantity and batch mark of each batch of such other drug manufactured by him and the disposition thereof; that he will make such records available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such disposition, and that he will accord full opportunity to such officer or employee to make inventories of stocks on hand and otherwise check the correctness of such records; and

(3) A written agreement signed by the person who will own the drug after its manufacture is completed that he will request certification of each batch thereof unless it is exempt under section 801 (d) of the act or §§ 146.18, 146.19, 146.21, or 146.23, and that he will not remove any of such drug from such establishment unless it complies with section 502 (l) of the act or is so exempt or is returned to him for labeling.

When the Commissioner finds, after giving notice and opportunity for hearing, that such application contains any untrue statement of a material fact or that any provision of any such agreement has been violated he may revoke such permit.

(c) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is the operator of such establishment, shall become void at the beginning of the act of removing or offering to remove such shipment or

delivery or any part thereof from such establishment, prior to its use in the manufacture of another drug, unless it is exempt under section 801 (d) of the act.

(d) An exemption of a shipment or other delivery under paragraph (a) of this section, in case the person who introduced such shipment or delivery into interstate commerce is not the operator of such establishment, shall expire at the beginning of the act of removing or offering to remove such shipment or delivery or any part thereof from such establishment, prior to its use in the manufacture of another drug, unless it is exempt under section 801 (d) of the act.

§ 146.23 Exemptions for investigational use.

(a) A shipment or other delivery of a drug shall be exempt from section 502(l) of the act if all of the following requirements are complied with:

(1) The label of such drug bears the batch mark and the statement "Caution: Limited by Federal law to investigational use only."

(2) Such shipment or delivery is made only to, and solely for investigational use by or under the direction of, an expert qualified by scientific training and experience to investigate the safety or efficacy of such drug.

(3) The person who introduced such shipment or delivery into interstate commerce keeps complete records showing the date, quantity, and batch mark of each such shipment and delivery.

(4) Such person, prior to making such shipment or delivery, obtains a statement signed by such expert showing that he has adequate facilities for the investigation to be conducted by him, and that such drug will be used solely by him or under his direction for the investigation. Such person shall keep such statement. This subparagraph shall not apply when such shipment or delivery is made to an agency of the Government of the United States (including the National Research Council) or to any State or municipality whose official functions involve investigations of such drugs by such experts.

(5) Such person makes all documents referred to in subparagraphs (3) and (4) of this paragraph available to any officer or employee of the Food and Drug Administration at any reasonable hour within three years after the date of such shipment or delivery.

(b) A shipment or other delivery of a drug which is being imported or offered for import into the United States shall be exempt from section 502 (l) of the act if all the following requirements are complied with:

(1) The label of such drug bears the batch mark and the statement "Caution: Limited by Federal law to investigational use only."

(2) The importer of such shipments or deliveries is an agent of the foreign exporter, residing in the United States, or the operator of an establishment in the United States which has facilities for regularly investigating the safety or efficacy of such drugs, which facilities are manned by experts qualified by scientific training and experience to conduct such investigation.

(3) Such operator uses such drug solely for such investigation in such establishment, or such operator or agent otherwise disposes of such drug only to, and solely for, investigational use by or under the direction of such an expert other than one in such an establishment.

(4) Such importer, prior to disposing of any of such drug to such an expert, obtains a statement signed by such expert showing that he has adequate facilities for the investigation to be conducted by him, and that such drug will be used solely by him or under his direction for the investigation. Such importer shall keep such statement. This subparagraph shall not apply to any shipment or delivery or part thereof disposed of by such importer to an agency of the Government of the United States (including the National Research Council) or to any State or municipality whose official functions involve investigations of such drugs by such experts.

(5) Such importer who introduced such shipment or delivery into interstate commerce keeps complete records showing the date, quantity, and batch mark of each such shipment and delivery.

(6) Such importer makes all documents referred to in subparagraphs (4) and (5) of this paragraph available to any officer or employee of the Food and Drug Administration at any reasonable hour within 3 years after the date of such shipment or delivery by such importer.

(c) An exemption under paragraph (a) or (b) of this section shall become void ab initio if any record or statement required by such paragraph to be kept and made available for inspection is not kept or made available as so required.

(d) An exemption under paragraph (a) or (b) of this section shall expire with respect to any exempted shipment or delivery or part thereof which has been supplied to an expert who has signed the statement referred to in paragraph (a) (4) or (b) (4) of this section and which is used otherwise than in accordance with such signed statement.

(e) An exemption under paragraph (b) of this section shall become void ab initio if the exempted shipment or delivery or any part thereof is disposed of otherwise than as provided by subparagraph (3) of such paragraph.

(f) No exemption under paragraph (b) of this section shall apply to any shipment or delivery to such importer if such importer, within 3 years prior to the offering of such shipment or delivery for import, has caused an exemption to become void as provided by paragraph (c) or (e) of this section.

§ 146.24 Penicillin powder for diagnostic use; streptomycin powder for diagnostic use; dihydrostreptomycin powder for diagnostic use; chlortetracycline hydrochloride powder for diagnostic use; tetracycline hydrochloride powder for diagnostic use; chloramphenicol powder for diagnostic use; bacitracin powder for diagnostic use.

CROSS-REFERENCES: For tests and methods of assay and certification of antibiotic sensitivity discs for laboratory diagnosis of disease, see §§ 147.1 and 147.2 of this chapter.

Dry powder of penicillin, streptomycin, dihydrostreptomycin, chlortetracycline hydrochloride, tetracycline hydrochloride, chloramphenicol, or bacitracin, with or without suitable buffer substances and diluents, packaged for dispensing and intended for use solely in laboratory procedures in connection with the diagnosis or treatment of disease and conspicuously so labeled shall be exempt from the certification requirements of sections 502(l) and 507 of the act if each complies with all of the following conditions:

(a) The potency and moisture content of the antibiotic used in the manufacture of the powder and the moisture content of the powder comply with the standards prescribed for the antibiotic by §§ 146a.24, 146b.101, 146b.103, 146c.-201, 146c.218, 146d.301, and 146e.401 of this chapter.

(b) It is packaged in immediate containers that are tight containers as defined by the U.S.P. Each such container shall contain not less than 10 milligrams.

(c) Each package bears on the label or labeling of its outside wrapper or container and the immediate container the following:

(1) The statement "Diagnostic reagent. For professional use only."

(2) The number of milligrams or grams contained in each immediate container and the potency per milligram.

(3) The batch mark.

(4) The statement "Expiration date _____," the blank being filled in with the date that does not exceed the expiration date authorized for the antibiotic salt by this chapter.

(d) The circular or other labeling within or attached to the package bears directions adequate for the use of such drug.

§ 146.25 Antibiotic drugs for use in medicated animal feed (antibiotic medicated feed premixes; antibiotic medicated feed concentrates that must be diluted with feed ingredients before they are fed).

Any certifiable antibiotic drug subject to the regulations in this chapter or any combination of two or more such drugs, with or without those ingredients specified in § 146 26, intended for use solely as an ingredient in the manufacture of animal feed and conspicuously so labeled shall be exempt from the requirements of sections 502(l) and 507 of the act if it complies with the following conditions:

(a) It contains one or more suitable denaturants that make it unfit for human use; and

(b) Its labeling is such that animal feed mixed according to the directions contained therein complies with the requirements of § 146.26.

(c) It contains no substance for which § 146.26 requires exemptions from certification of the medicated feeds in which it is used as an ingredient, unless prior to shipment in commerce:

(1) The manufacturer obtained a permit from the Commissioner issued under the provisions of § 146.22 authorizing shipment for manufacturing use to such establishment, or

(2) The operator of the establishment where such drug is to be mixed or diluted meets all the conditions for exemption from certification of the medicated feed established by the applicable

provisions of § 146.26, including when required, the submission to, and acceptance by the Commissioner of adequate information of the kind required by § 146.7, to establish the safety and efficacy of the finished medicated feed and to guarantee its identity, strength, quality, and purity.

§ 146.26 Animal feed containing penicillin; animal feed containing streptomycin; animal feed containing dihydrostreptomycin; animal feed containing chlortetracycline; animal feed containing tetracycline; animal feed containing bacitracin; animal feed containing feed grade zinc bacitracin; animal feed containing bacitracin methylene disalicylate.

Animal feed containing penicillin, streptomycin, dihydrostreptomycin, chlortetracycline, tetracycline, bacitracin, feed grade zinc bacitracin, or bacitracin methylene disalicylate, or any combination of two or more of these, with or without added suitable vitamin substances, shall be exempt from the requirements of sections 502(1) and 507 of the act under the conditions set forth in any one of the following paragraphs of this section:

(a) It is intended for use solely as an animal feeding supplement, it is conspicuously so labeled, and it is manufactured with or without one, but only one, of the following ingredients in a quantity, by weight of feed, as hereinafter indicated:

(1) Arsanilic acid: Not less than 0.005 percent and not more than 0.01 percent.

(2) Sodium arsanilate: Not less than 0.005 percent and not more than 0.01 percent.

(3) 3-Nitro-4-hydroxyphenol arsonic acid: Not less than 0.0025 percent and not more than 0.0075 percent.

(4) Furazolidone: 0.00083 percent.

(5) Furazolidone 0.00083 percent with or without nitrofurazone 0.0056 percent and/or 3-nitro-4-hydroxyphenylarsonic acid not less than 0.0025 percent and not more than 0.0075 percent.

(b) It is intended for use in the conditions set forth in any one of the following subparagraphs of this paragraph:

(1) It is intended for use solely in the prevention of coccidiosis outbreaks in poultry flocks, its labeling bears adequate directions and warnings for such use, and it contains one, but only one, of the following ingredients in a quantity, by weight of feed, as hereinafter indicated:

(i) Sulfaquinoxaline: Not less than 0.0125 percent (or if it is intended solely for the prevention of the intestinal coccidia *E. acervalina* in poultry laying flocks, not less than 0.005 percent) and not more than 0.025 percent.

(ii) Nitrophenide: Not less than 0.0125 percent and not more than 0.025 percent.

(iii) Nitrofurazone: 0.0056 percent.

(iv) N'-acetyl-N'-(4-nitrophenyl) sulfanilamide 0.03 percent and 3-nitro-4-hydroxyphenylarsonic acid 0.000 percent.

(v) Furazolidone 0.00083 percent, nitrofurazone 0.0056 percent, with or without 3-nitro-4-hydroxyphenylarsonic acid not less than 0.0025 percent and not more than 0.0075 percent.

(2) It is intended for use solely in the control of coccidiosis outbreaks in poultry flocks, its labeling bears adequate directions and warnings for such use, and it contains one, but only one, of the following ingredients in a quantity, by weight of feed, as hereinafter indicated:

(i) Sulfaquinoxaline: Not less than 0.033 percent and not more than 0.10 percent.

(ii) Nitrophenide: 0.05 percent.

(iii) Nitrofurazone: 0.0112 percent.

(3) It is intended for use solely in the prevention of outbreaks of histomoniasis ("blackhead") in turkey flocks, its labeling bears adequate directions and warnings for such use, and it contains one, but only one, of the following ingredients in a quantity, by weight of feed, as hereinafter indicated:

(i) 2-Amino-5-nitrothiazole: 0.05 percent.

(ii) 4-Nitrophenylarsonic acid: 0.025 percent.

(4) It is intended for use solely in the control of outbreaks of histomoniasis ("blackhead") in turkey flocks, its labeling bears adequate directions and warnings for such use, and it contains 2-amino-5-nitrothiazole in a quantity, by weight of feed, of 0.10 percent.

(5) It is intended for use solely as an anthelmintic for poultry or swine, its labeling bears adequate directions and warnings for such use, and it contains one, but only one, of the following ingredients in a quantity, by weight of feed, as hereinafter indicated:

(i) di-*N*-Butyl tin dilaurate 0.07 percent, nicotine 0.03 percent, and phenothiazine 0.29 percent.

(ii) Nicotine 0.067 percent, phenothiazine 0.60 percent, and 2,2'dihydroxy-5,5'dichlorodiphenylmethane 0.28 percent.

(iii) Phenothiazine, not less than 0.3 percent and not more than 1.0 percent, and nicotine, not less than 0.03 percent and not more than 0.07 percent.

(iv) Phenothiazine, not less than 0.3 percent and not more than 1.0 percent.

(v) Nicotine, not less than 0.03 percent and not more than 0.07 percent.

(vi) Sodium fluoride 0.3 percent and sodium sulfate 2.0 percent.

(vii) Cadmium anthranilate, 0.044 percent.

(viii) Cadmium oxide, 0.015 percent.

(ix) Sodium fluoride, not less than 0.5 percent and not more than 1.0 percent.

(x) Piperazine dihydrochloride, not less than 0.18 percent and not more than 0.72 percent (piperazine base 0.1 percent to 0.4 percent).

(xi) Piperazine phosphate monohydrate, not less than 0.23 percent and not more than 0.92 percent (piperazine base 0.1 percent to 0.4 percent).

(xii) Piperazine sulfate, not less than 0.21 percent and not more than 0.85 percent (piperazine base 0.1 percent to 0.4 percent).

(xiii) Piperazine monohydrochloride, not less than 0.13 percent and not more than 0.52 percent (piperazine base 0.1 percent to 0.4 percent).

(xiv) di-*N*-Butyl tin dilaurate 0.07 percent, piperazine sulfate 0.12 percent, and phenothiazine 0.29 percent.

(6) It is intended for use solely in the prevention of chronic respiratory disease (air-sac infection) and hexamitiasis in poultry, bacterial swine enteritis, and/or bacterial calf diarrhea; its labeling bears adequate directions and warnings for such use, and it contains, per ton of feed, not less than 50 grams of chlortetracycline or oxytetracycline or a combination of such drugs; or, if it is intended for use solely as an aid in the prevention of bacterial swine enteritis, it contains a combination of 37.5 grams of streptomycin and 7.5 grams of penicillin per ton of feed. If it contains not less than 100 grams of chlortetracycline or oxytetracycline or a combination of such drugs per ton of feed, it may also be represented for use as an aid in the prevention of synovitis in poultry. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section.

(7) (i) It is intended for use solely as a treatment for chronic respiratory disease (air-sac infection), infectious sinusitis, blue comb (nonspecific infectious enteritis, mud fever), and hexamitiasis in poultry, and/or bacterial swine enteritis; its labeling bears adequate directions and warnings for such use; and it contains, per ton of feed, not less than 100 grams of chlortetracycline or oxytetracycline or a combination of such drugs or not less than 75 grams of streptomycin and 15 grams of penicillin. If it contains not less than 200 grams of chlortetracycline or oxytetracycline or a combination of such drugs per ton of feed, it may also be represented for use as an aid in the control of synovitis in poultry. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section. If it is intended for use solely in poultry, it may contain 0.1 percent of para-aminobenzoic acid or the sodium or potassium salt of para-aminobenzoic acid; or if it is intended for continuation of coccidiosis prevention it shall contain, in the amount specified, one of the ingredients prescribed by subparagraph (1) of this paragraph. If it is intended for use solely in the treatment of the diseases of chickens described in this subparagraph, it contains, per ton of feed, not less than 100 grams and not more than 200 grams of chlortetracycline and it contains not less than 0.4 percent and not more than 0.8 percent of dietary calcium, then representations may be made in its labeling to the effect that the reduced amount of calcium aids in increasing the concentrations of the antibiotic in the blood of treated birds; the labeling of such medicated feed shall include that required by § 121.208 of this chapter.

(ii) It is also intended for use in the prevention and control of coccidiosis in chickens caused by E. tenella and E. necatrix; its labeling bears adequate directions and warnings for such use (including the directions and warnings required by subdivision (i) of this subparagraph), and it contains, per ton

of feed, 200 grams of chlortetracycline and 0.8 percent of dietary calcium.

(iii) It is also intended for use in the treatment of coccidiosis in chickens caused by E. tenella and E. necatrix; its labeling bears adequate directions and warnings for such use (including the directions and warnings required by subdivision (i) of this subparagraph); and it contains, per ton of feed, 200 grams of chlortetracycline and 0.4 percent to 0.55 percent of dietary calcium.

(8) It is intended for use solely in the prevention of coccidiosis and hexamitiasis outbreaks in turkey flocks, its labeling bears adequate directions and warnings for such use, and it contains di-*N*-butyl tin dilaurate in a quantity, by weight of feed, of 0.0375 percent.

(9) It is intended for use solely in the prevention of chronic respiratory disease (air-sac infection), infectious sinusitis, and blue comb (nonspecific infectious enteritis) in poultry and/or bacterial swine enteritis; its labeling bears adequate directions and warnings for such use, and it contains, per ton of feed, the equivalent of not less than 50 grams of bacitracin or 50 grams of penicillin (unless it is intended for bacterial swine enteritis) or 50 grams of a combination of the two drugs, except that if it contains the combination drug and it is intended for the prevention of bacterial swine enteritis it shall contain the equivalent of not less than 25 grams of bacitracin. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section.

(10) It is intended for use solely in the treatment of chronic respiratory disease (air-sac infection), infectious sinusitis, and blue comb (nonspecific infectious enteritis) in poultry and/or bacterial swine enteritis; its labeling bears adequate directions and warnings for such use, and it contains, per ton of feed, the equivalent of not less than 100 grams of bacitracin or 100 grams of penicillin (unless it is intended for bacterial swine enteritis) or 100 grams of a combination of the two drugs, except that if it contains the combination drug and it is intended for the treatment of bacterial swine enteritis it shall contain the equivalent of not less than 50 grams of bacitracin. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section.

(11) It is intended for use solely as a treatment for bacterial swine enteritis caused by Salmonella choleraesuis, its labeling bears adequate directions and warnings for such use, and it contains nitrofurazone in a quantity, by weight of feed, of 0.056 percent.

(12) It is intended for use solely in the prevention of coccidiosis, chronic respiratory disease (air-sac infection) and hexamitiasis in poultry; its labeling bears adequate directions and warnings for such use; and it contains, in the amount specified, one of the ingredients prescribed by subparagraph (1) of this paragraph and not less than 50 grams of chlortetracycline per ton of feed. When intended for such uses it may also contain oxytetracycline in a quantity not less than 50 grams per ton of feed.

(13) It is intended for use solely in the prevention or treatment of chronic respiratory disease (air-sac infection) and infectious sinusitis in poultry; its labeling bears adequate directions and warnings for such use; and it contains not less than 0.1 percent para-aminobenzoic acid or the sodium or potassium salt of para-aminobenzoic acid.

(14) It is intended solely as an aid in the prevention and control of losses due to low-grade bacterial enteritis in mink; its labeling bears adequate directions and warnings for such use; and it contains not less than 5.7 grams of chlortetracycline, 1.0 gram of bacitracin, and 0.75 gram of penicillin (with or without oxytetracycline) per ton of feed.

(15) It is intended for use solely as an aid in the prevention or treatment or to lessen the morbidity in poultry in outbreaks of fowl typhoid, pullorum, the paratyphoids, infectious arthritis due to a filterable agent, histomoniasis (blackhead), hexamitiasis, quail disease (ulcerated enteritis), paracolon infection, avian infectious hepatitis, and coccidiosis, its labeling bears adequate directions and warnings for such use; and it contains the following quantities of furazolidone, by weight of feed, for the conditions indicated:

(i) For the prevention of fowl typhoid, pullorum, and the paratyphoids in birds older than 2 weeks: 0.0055 percent.

(ii) For the prevention of the diseases listed in subdivision (i) of this subparagraph in birds younger than 2 weeks, and for the treatment of these same conditions in birds regardless of age: 0.011 percent.

(iii) For the prevention of histomoniasis (blackhead) paracolon infection and infectious arthritis due to a filterable agent, and for the prevention and treatment of hexamitiasis, and quail disease (ulcerative enteritis): 0.011 percent.

(iv) For the treatment of histomoniasis (blackhead) paracolon infection, and avian infectious hepatitis of chickens, and to lessen the morbidity in outbreaks of infectious arthritis due to a filterable agent: 0.022 percent.

(v) For the prevention of coccidiosis in chickens: 0.0055 percent.

(vi) For the control of coccidiosis in chickens: 0.011 percent.

(16) (i) It is intended for use solely in the prevention of chronic respiratory disease (air-sac infection); its labeling bears adequate directions and warnings for such use; and it contains not less than 50 grams of chlortetracycline or oxytetracycline or a combination of these two drugs per ton of feed. When intended for such use, it may also contain the equivalent of not less than 50 grams of bacitracin per ton of feed.

(ii) It is also intended for the prevention or treatment of the diseases of poultry specified in subparagraph (15) of this paragraph; it contains one of the ingredients in the amount and under the conditions set forth in subdivision (i) of this subparagraph; and it contains furazolidone in the amount specified in subparagraph (15) of this paragraph.

(17) (i) It is intended for use solely as an aid in the treatment of chronic respiratory disease (air-sac infection), infectious sinusitis, blue comb (nonspecific infectious enteritis, mud fever) in poultry; its labeling bears adequate directions and warnings for such use; and it contains not less than 100 grams of chlortetracycline or oxytetracycline or a combination of these two drugs per ton of feed. When intended for such use, it may also contain the equivalent of not less than 100 grams of bacitracin per ton of feed.

(ii) It is also intended for the prevention or treatment of the diseases of poultry specified in subparagraph (15) of this paragraph; it contains one of the ingredients in the amount and under the conditions set forth in subdivision (i) of this subparagraph; and it contains furazolidone in the amount specified in subparagraph (15) of this paragraph.

(18) (i) It is intended for use solely in the prevention of outbreaks of coccidiosis in poultry flocks, and it contains nicarbazin (4,4'-dinitrocarbanilide complex with 2-hydroxy-4-6-dimethylpyrimidine) in a quantity, by weight of feed, of not less than 0.01 percent and not more than 0.02 percent, or arsenosobenzene in a quantity, by weight of feed, of 0.002 percent, or 2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine in a quantity, by weight of feed, of 0.00075 percent and sulfaquinoxaline in a quantity, by weight of feed, of 0.0075 percent, or 2,2'dihydroxy-3,3',5,5'-tetrachlorodiphenyl sulfide (bithionol) 0.05 percent and 4,6-diamino-1-(4-methylmercaptophenyl)-1,2-dihydro-2,2-dimethyl-1,3,5-triazine hydrochloride (methiotriazamine) 0.01 percent; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug or the methods used in its manufacturing, processing, or packaging or the facilities and controls used for such manufacturing, processing, or packaging, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information describing such proposed changes, and such amendment has been accepted by the Commissioner.

(ii) It is also intended for the prevention or treatment of the diseases of poultry specified in subparagraphs (6) and (7) and/or (9) and (10) or (16) and (17) of this paragraph, it contains one of the ingredients in the amount and under the conditions set forth in subdivision (i) of this subparagraph, and it contains the ingredients in the amounts specified in subparagraphs (6) and (7) and/or (9) and (10) or (16) and (17) of this paragraph, except that the coccidiostat shall be only one of those specified in subdivision (i) of this subparagraph.

(iii) It is intended for use in the diseases specified in subdivisions (i), (ii) and (iv) of this subparagraph, it con-

tains ingredients in the amounts and under the conditions specified in those subdivisions, and it contains one, but only one, of the ingredients prescribed by paragraph (a) of this section and in the amounts specified in that paragraph.

(iv) It is also intended for use as an adjunct in reducing the tapeworm and large roundworm burden of chickens so treated, it contains 2,2'-dihydroxy-3,3',5,5,'-tetrachlorodiphenyl sulfide (bithionol), and 4,6-diamino-1-(4-methylmercaptophenyl)-1,2-dihydro-2,2-dimethyl-1,3,5-triazine hydrochloride (methiotriazamine), in the amounts and under the conditions set forth in subdivision (i) of this subparagraph.

(19) (i) It is intended for use solely in the prevention or control of outbreaks of histomoniasis ("blackhead") in turkey flocks, and it contains 2-acetylamino-5-nitrothiazole in a quantity, by weight of feed, of 0.015 percent if intended for the prevention of the disease, or 0.05 percent if intended for the control of the disease, and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition of such drug, or the methods used in, and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner.

(ii) It is intended for use in the disease specified in subdivision (i) of this subparagraph; it contains the ingredient in the amount and under the conditions specified in that subdivision; and it contains one, but only one, of the ingredients prescribed by paragraph (a) of this section and in the amounts specified in that paragraph.

(20) It is intended as an aid in stimulating growth, the prevention of coccidiosis, large roundworms and tapeworms in chickens and turkeys and the prevention of hexamitiasis in turkeys, and it contains in a quantity, by weight of feed, acetyl (*p*-nitrophenyl) sulfanilamide 0.03 percent, dibutyl tin dilaurate 0.02 percent, dinitrodiphenylsulfonylethylenediamine 0.02 percent, and 3-nitro-4-hydroxyphenylarsonic acid 0.0075 percent.

(21) (i) It is intended for promoting distribution of fat in chickens and turkeys; its labeling bears adequate directions and warnings for such use, including a warning against its use in laying hens and a warning that its use must be discontinued 24 hours before the treated chickens or turkeys are slaughtered for human consumption; and it contains dienestrol diacetate in a quantity, by weight of feed, of not less than 0.0023 percent and not more than 0.007 percent; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug or the methods used in and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information describing such proposed changes, and such amendment has been accepted by the Commissioner.

(ii) It is also intended for the prevention or treatment of the diseases of poultry specified in subparagraphs (6) and (7) of this paragraph, it contains dienestrol diacetate in the amounts and under the conditions set forth in subdivision (i) of this subparagraph, and it contains the antibiotics in the amounts specified in subparagraphs (6) and (7) of this paragraph.

(iii) It is also intended for continuation of coccidiosis prevention in poultry, it contains dienestrol diacetate in the amounts and under the conditions set forth in subdivision (i) of this subparagraph, and it contains one, but only one, of the ingredients prescribed by subparagraph (1) of this paragraph and in the amounts specified in that subparagraph, or it contains one, but only one, of the coccidiostats prescribed by subparagraph (18) of this paragraph, and in the amounts specified in that subparagraph.

(iv) It is also intended for use in the prevention of outbreaks of histomoniasis (blackhead) in turkey flocks, it contains dienestrol diacetate in the amounts and under the conditions set forth in subdivision (i) of this paragraph, and it contains one, but only one, of the ingredients prescribed by subparagraph (3) of this paragraph and in the amounts specified in that subparagraph.

(v) It is also intended for the prevention or treatment of the diseases of poultry specified in subparagraph (15) of this paragraph, it contains dienestrol diacetate in the amounts and under the conditions set forth in subdivision (i) of this subparagraph, and it contains furazolidone in the amounts specified in subparagraph (15) of this paragraph.

(vi) It is intended for use in the diseases specified in subdivisions (i), (ii), (iii), (iv) and (v), of this subparagraph, it contains ingredients in the amounts and under the conditions specified in those subdivisions, and it contains one, but only one, of the ingredients prescribed by paragraph (a) of this section, and in the amounts specified in that paragraph. If it contains one of the arsenic compounds prescribed in paragraph (a) of this section, its labeling must bear a warning that it must be discontinued 5 days (instead of 24 hours as required in this subparagraph) before the treated chickens or turkeys are slaughtered for human consumption.

(22) (i) It is intended for use solely in the control of outbreaks of coccidiosis in poultry flocks and it contains in a quantity, by weight of feed, not less than 0.003 percent and not more than 0.006 percent of 2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine and not less than 0.01 percent and not more than 0.02 percent of sulfaquinoxaline, and there has been submitted to the Commissioner, in triplicate, the information referred to in § 146.7, as well as any additional information necessary to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug or the methods used in its manufacturing, processing, or repackaging, or the facilities and controls used for such manufacturing, processing, or repackaging, unless the person who obtains the exemption has submitted to the Commissioner, in triplicate, amended information describing such proposed changes and such amendment has been accepted by the Commissioner.

(ii) It is intended for use in the disease specified in subdivision (i) of this subparagraph, it contains the ingredients in the amounts and under the conditions specified in that subdivision, and it contains one, but only one, of the ingredients prescribed by paragraph (a) of this section and in the amounts specified in that paragraph.

(23) It is intended for use solely as an aid in the reduction of losses due to enterotoxemia in sheep; its labeling bears adequate directions and warnings for such use; and it contains not less than 20 grams of chlortetracycline per ton of feed.

(24) It is intended for use in the maintenance of weight gains of swine in the presence of atrophic rhinitis or as an aid in reducing the incidence of cervical abscesses in swine; its labeling bears adequate directions and warnings for such use; and it contains not less than 50 grams of chlortetracycline per ton of feed.

(25) It is intended for use as an aid in the reduction of bacterial diarrhea in beef cattle or as an aid in the prevention or treatment of bacterial pneumonia and shipping fever (hemorrhagic septicemia) or as an aid in reduction of losses due to respiratory infection (infectious rhinotracheitis-shipping fever complex) or as an aid in the prevention of foot rot in cattle or as an aid in the prevention of anaplasmosis in cattle or as an aid in the prevention of liver abscesses in feed-lot beef cattle; its labeling bears adequate directions and warnings for such uses; and it contains the following quantities of chlortetracycline, by weight of feed, for the conditions indicated:

(i) For the prevention of anaplasmosis: 0.5 milligram per pound of body weight per day.

(ii) For the prevention of foot rot in cattle; 0.1 milligram per pound of body weight per day.

(iii) For the prevention or treatment of foot rot in cattle: 0.1 milligram per pound of body weight per day.

(iii) As an aid in the reduction of bacterial diarrhea in beef cattle: 0.1 milligram per pound of body weight per day.

(iv) As an aid in the prevention or treatment of bacterial pneumonia and

shipping fever (hemorrhagic septicemia) or as an aid in reduction of losses due to respiratory infection (infectious rhinotracheitis-shipping fever complex) in cattle: 350 milligrams per head per day, except that if it is intended for use for more than 30 days it may contain chlortetracycline, in a quantity by weight of feed to provide 70 milligrams per head per day.

(v) As an aid in the prevention of liver abscesses in feed-lot beef cattle: 70 milligrams per head per day.

(26) (i) It is intended for use solely for accelerating weight gains in beef cattle, and it contains a quantity of diethylstilbestrol adequate to provide not more than 10 milligrams per head per day when fed in accordance with the directions for use that accompany the feed, and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug or the methods used in its manufacturing, processing, packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information describing such proposed changes, and such amendment has been accepted by the Commissioner.

(ii) It is also intended for the prevention or treatment of the diseases specified in subparagraph (25) of this paragraph, it contains diethylstilbestrol in the amount and under the conditions set forth in subdivision (i) of this subparagraph, and it contains the antibiotic in the amount specified in subparagraph (25) of this paragraph.

(27) It is intended for use as an aid in maintaining or increasing egg production, hatchability of eggs, prevention of early mortality of chicks when due to organisms that are sensitive to chlortetracycline, and for improving feed efficiency as related to egg production; its labeling bears adequate directions and warnings for such use; and it contains not less than 50 grams of chlortetracycline per ton of feed, except that if it is intended for use in the presence of disease outbreaks it shall contain not less than 100 grams of chlortetracycline per ton of feed.

(28) It is intended for use solely as an aid in the prevention or control of outbreaks of histomoniasis ("blackhead") in poultry flocks, and it contains carbasone in a quantity, by weight of feed, of not less than 0.05 percent and not more than 0.1 percent (except that if it is intended for prevention of histomoniasis in turkey flocks it contains not less than 0.0375 percent) and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition of such drug, or the methods used in and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner.

(29) It is intended for use solely as an aid in reducing the incidence of bacterial diarrhea in laboratory mice; its labeling bears adequate directions and warnings for such use; and it contains not less than 100 grams of chlortetracycline per ton of feed.

(30) It is intended for use as an aid in maintaining or increasing egg production of chickens, hatchability of eggs, prevention of early mortality of chicks when due to organisms that are sensitive to streptomycin and penicillin, and for improving feed efficiency of chickens or turkeys; its labeling bears adequate directions and warnings for such use; and it contains, per ton of feed, 18.75 grams of streptomycin and 3.75 grams of penicillin; except that if it is intended for use in the presence of disease, as an aid in maintaining or increasing hatchability of eggs, or for the prevention of early mortality of chicks, it contains 75 grams of streptomycin and 15 grams of penicillin per ton of feed.

(31) It is intended for use in nursing sows to stimulate milk flow; it contains 100 milligrams of iodinated casein per pound; and its labeling bears information that it is to be administered as the complete ration for 3 days before farrowing and until pigs are weaned. It may also be intended for use in the prevention or treatment of bacterial swine enteritis if it contains the antibiotics in the amounts prescribed by this section for that disease.

(32) (i) It is intended for use as an aid in the control of infestation of large roundworms (Ascaris suis), nodular worm (Oesophagostemum dentatum), and whipworm (Trichuris suis) in swine; its labeling bears adequate directions and warnings for such use, including a warning that its use must be discontinued 48 hours before the treated swine are slaughtered for human consumption. If it is a complete feed it contains 6,000 units (6 milligrams) of hygromycin B (produced by the growth of Streptomyces hygroscopicus) per pound, or if it is a hygromycin B feed supplement or premix it contains not more than 8,000,000 units (8 grams) of hygromycin B per pound. It contains less than 50 grams of antibiotics per ton of finished feed. If it is a hygromycin B feed supplement or premix and it contains more than 8,000,000 units of hygromycin B per pound, it shall be exempt from certification only if there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. Such exemption shall expire at the beginning of any act changing the composition or labeling of such drug or the methods used in its manufacturing, processing, or packaging, or the facilities and controls used for such manufacturing, processing, or packaging, unless the person who obtained the exemption has submitted to the Commissioner (in triplicate) amended information describing such proposed changes, and such amendment has been accepted by the Commissioner. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section. If it contains one of the arsenic compounds prescribed in such paragraph, its labeling must bear a warning that it must be discontinued 5 days (in lieu of 48 hours as required in this subparagraph) before the treated swine are slaughtered for human consumption.

(ii) It is also intended for the prevention or treatment of bacterial swine enteritis as specified in subparagraphs (9) and (10) of this paragraph; it contains hygromycin B in the amounts and under the conditions set forth in subdivision (i) of this subparagraph; and it contains the drugs in the amount specified in subparagraphs (9) and (10) of this paragraph. If it contains one of the arsenic compounds prescribed in paragraph (a) of this section, its labeling must bear the warning specified in subdivision (i) of this subparagraph.

(iii) It is also intended for the prevention and treatment of bacterial swine enteritis, it contains hygromycin B in the amounts and under the conditions set forth in subdivision (i) of this subparagraph, and it contains penicillin and streptomycin in the amounts specified in subparagraphs (6) and (7) of this paragraph. If it contains one of the arsenic compounds prescribed in paragraph (a) of this section, its labeling must bear the warning specified in subdivision (i) of this subparagraph.

(iv) It is also intended for the prevention and treatment of bacterial swine enteritis, for the maintenance of weight gains of swine in the presence of atrophic rhinitis and for reducing the incidence of cervical abscesses in swine, it contains hygromycin B in the amounts and under the conditions set forth in subdivision (i) of this subparagraph, and it contains, per pound of feed, 0.025 gram (50 grams per ton), of the chlortetracycline; except that if it is intended for use in the treatment of bacterial swine enteritis it shall contain, per pound of feed, 0.05 gram (100 grams per ton), of chlortetracycline.

(33) It is intended for use as an aid in reducing the incidence and severity of bloat in cattle on legume pastures; it contains a quantity of procaine penicillin that, when used as directed in the labeling, is sufficient to furnish each treated bovine animal not less than 75,000 units as a single daily dose; and, if the drug supplement used to prepare the medicated feed contains more than 2 percent moisture, its manufacturer has submitted to the Commissioner information adequate to prove its stability for 6 months under customary conditions of purchase and use.

(34) It is intended for use as an aid in the reduction of bacterial diarrhea in dairy cattle or as an aid in reduction of losses due to respiratory infection (in-

fectious rhinotracheitis—shipping fever complex) or as an aid in the prevention of foot rot in cattle; its labeling bears adequate directions and warnings for such uses; and it contains the following quantities of chlortetracycline, by weight of feed, for the conditions indicated:

(i) For the prevention of foot rot and as an aid in the reduction of bacterial diarrhea in dairy cattle: 0.1 milligram per pound of body weight per day.

(ii) As an aid in reduction of losses due to respiratory infection (infectious rhinotracheitis—shipping fever complex) in dairy cattle: 0.1 milligram per pound of body weight per day, except that if it is intended for use for more than 30 days it may contain chlortetracycline, in a quantity by weight of feed to provide 70 milligrams per head per day.

(35) It is intended for use solely as an aid in the prevention of coccidiosis and as an aid in stimulating growth in chicken flocks; its labeling bears adequate directions and warnings for such use, including a warning against its use in laying hens and a warning that its use must be discontinued 5 days before the treated chickens are slaughtered for human consumption; and it contains in a quantity, by weight of feed, 0.03 percent acetyl (paranitrophenyl) sulfanilamide, 0.025 percent 3,5-dinitrobenzamide, and 0.005 percent 3-nitro-4-hydroxyphenylarsonic acid; it contains less than 50 grams of antibiotics per ton of feed; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition of such drug, or the methods used in, and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner.

(36) It is intended for use solely as an aid in stimulating growth in chickens and turkeys and as an aid in the prevention of outbreaks of histomoniasis (blackhead) in chickens and turkeys and hexamitiasis in turkeys; its labeling bears adequate directions and warnings for such use, including a warning against its use in laying hens and a warning that its use must be discontinued 24 hours before the treated chickens or turkeys are slaughtered for human consumption; and it contains nithiazide (1-ethyl-3-(5-nitro-2-thiazolyl) urea) in a quantity, by weight of feed, of not less than 0.0125 percent and not more than 0.04 percent; it contains less than 50 grams of antibiotics per ton of feed; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug or the methods used in and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information describing such proposed changes, and such amendment has been accepted by the Commissioner. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section. If it contains one of the arsenic compounds prescribed in paragraph (a) of this section, its labeling must bear a warning that it must be discontinued 5 days (instead of 24 hours as required in this subparagraph) before the treated chickens or turkeys are slaughtered for human consumption.

(37) It is intended for use solely in the prevention of outbreaks of coccidiosis and as an aid in stimulating growth in chicken flocks; its labeling bears adequate directions and warnings for such use, including a warning against its use in laying hens and a warning that its use must be discontinued 4 days before the treated chickens are slaughtered for human consumption; and it contains glycarbylamide (4,5-imidazole-dicarboxamide) in a quantity, by weight of feed, of not less than 0.002 percent and not more than 0.006 percent; it contains less than 50 grams of antibiotics per ton of feed; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition of such drug, or the methods used in, and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section. If it contains one of the arsenic compounds prescribed in such paragraph, its labeling shall bear a warning that it must be discontinued 5 days (in lieu of 4 days as required in this subparagraph) before the treated chickens are slaughtered for human consumption.

(38) It is intended for use solely for accelerating weight gains in sheep; its labeling bears adequate directions and warnings for such use, including a warning that its use must be discontinued 48 hours before the treated animals are slaughtered for human consumption; it contains a quantity of diethylstilbestrol adequate to provide not more than 2 milligrams per head per day when fed in accordance with the directions for use that accompany the feed; it contains less than 50 grams of antibiotics per ton of feed; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug, or the methods used in its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information describing such proposed changes, and such amendment has been accepted by the Commissioner.

(39) It is intended for use solely as an aid in the prevention or treatment of fowl typhoid, paratyphoid, and pullorum disease and as an aid in stimulating growth in poultry flocks; its labeling bears adequate directions and warnings for such use, including a warning against its use in laying hens and a warning that its use must be discontinued 48 hours before the treated animals are slaughtered for human consumption; and it contains 3,5-dinitrobenzamide in a quantity, by weight of feed, of not less than 0.075 percent and not more than 0.15 percent; it contains less than 50 grams of antibiotics per ton of feed; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug, or the methods used in and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner. When intended for the uses specified in this subparagraph, it may also contain, in the amount specified, one, but only one, of the ingredients prescribed by paragraph (a) of this section. If it contains one of the arsenic compounds prescribed in paragraph (a) of

this section, its labeling must bear a warning that it must be discontinued 5 days (in lieu of 48 hours as required in this subparagraph) before the treated chickens or turkeys are slaughtered for human consumption.

(40) It is intended as an aid in maintaining or increasing egg production, hatchability of eggs, reduction of the effects of stress, prevention of early mortality of chicks, and reduction of the effects of diseases when due to organisms that are sensitive to bacitracin or to a mixture of bacitracin and penicillin, for maintaining appetite and for improving feed efficiency as related to egg production; its labeling bears adequate directions and warnings for such use; and it contains, per ton of feed, the equivalent of 50 grams of bacitracin or a mixture of 37.5 grams of bacitracin and 12.5 grams of penicillin when fed during the first 4 to 6 weeks of egg production, and not less than the equivalent of 10 grams of bacitracin or a mixture of 7.5 grams of bacitracin and 2.5 grams of penicillin when fed during the remainder of the laying period; except that if it is intended for use to increase egg hatchability or prevention of early mortality of chicks or for use in the presence of disease outbreaks or during periods of stress, it shall contain, per ton of feed, the equivalent of 100 grams of bacitracin or a mixture of 75 grams of bacitracin and 25 grams of penicillin.

(41) (i) It is intended for use as an aid in reducing the spread of leptospirosis in swine; it contains 200 grams of chlortetracycline per ton of feed; and its labeling bears information that it is to be administered continuously.

(ii) It is intended for use solely as an aid in reducing the shedding of leptospirae in swine and as an aid in reducing abortion rate and mortality of newborn pigs in the presence of leptospirosis; it contains 400 grams of chlortetracycline per ton of feed; and its labeling bears information that it is to be administered to the animals for 14 days.

(42) It is intended for use solely as an aid in the prevention of mycosis or in the treatment of mycotic diarrhea and as an aid in stimulating growth in turkey flocks; its labeling bears adequate directions and warnings for such use, including a warning that eggs are to be used for hatching purposes only, if such feed is intended for use in laying hens; and it contains nystatin in a quantity, by weight of feed, of 50 grams per ton if intended for the prevention of mycosis, or 100 grams per ton if intended for the treatment of mycotic diarrhea; it contains less than 50 grams of additional antibiotics per ton of feed; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug, or the methods used in and the facilities and controls used for its manufacturing, processing, and packaging or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information describing such proposed changes, and such amendment has been accepted by the Commissioner.

(43) It is intended for use solely as an aid in reducing the incidence of vibrionic abortion in breeding sheep; its labeling bears adequate directions and warnings for such use, including information that it is to be administered continuously during pregnancy; and it contains chlortetracycline in a quantity that, when administered as directed in its labeling, will provide a total daily dose of 80 milligrams per animal.

(44) (i) It is intended for the use solely as an aid in preventing outbreaks of coccidiosis in chickens and turkeys and as an aid in stimulating growth and improving feed efficiency in growing chickens and turkeys, and its labeling bears adequate directions and warnings for such use, including a warning against its use in laying hens. It contains, per ton of complete feed:

(*a*) Amprolium (1-(4-amino-2-*n*-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride), as follows:

(*1*) In a quantity, by weight of feed, of not less than 0.0125 percent and not more than 0.025 percent, if it is intended as an aid in preventing coccidiosis in chickens and turkeys; or

(2) In the following quantities, by weight of feed, under the conditions and for the ages of chickens indicated, if it is intended as an aid in preventing coccidiosis by developing immunity in chicken replacement flocks:

Growing conditions	Amount of amprolium in feed for birds, by age groups		
	Up to 5 weeks of age	From 5 to 8 weeks of age	From 8 to 14 weeks on range
	Percent	*Percent*	*Percent*
Severe exposure to coccidiosis	0.0125	0.008–0.0125	0.004–0.0125
Moderate exposure to coccidiosis	0.008–0.0125	0.006–0.0125	0.004–0.0125
Slight exposure to coccidiosis	0.004–0.0125	0.004–0.0125	0.004–0.0125

(*b*) The following quantities of antibiotics:

(*1*) Penicillin: Not less than 2.4 grams and not more than 50 grams; or

(2) Streptomycin: Not less than 30 grams and not more than 50 grams; or

(3) A combination of penicillin and streptomycin: Not less than 2.4 grams of penicillin and not less than 12 grams of streptomycin and not more than 50 grams of the combination drug; or

(4) Bacitracin (as feed-grade bacitracin, bacitracin methylene disalicylate, feed-grade zinc bacitracin, or feed-grade manganese bacitracin): Not less than 4 grams and not more than 50 grams; or

(5) A combination of bacitracin (as feed grade bacitracin, feed grade manganese bacitracin, feed grade zinc bacitracin, or bacitracin methylene disalicylate) and penicillin: Not less than 3 grams of bacitracin and not less than 0.6 gram of penicillin, and not more than 50 grams of the combination drug.

Provided, however, That such medicated complete feed has been prepared from a concentrated amprolium-antibiotic medicated feed that contained not more than 0.05 percent amprolium. If the complete medicated feed is prepared from a product of amprolium that contains more than 0.05 percent of the drug, it is exempt from certification only under the condition that there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug, or the methods used in and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtains the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner. Both concentrates and finished poultry feed containing amprolium must comply with all the requirements of § 121.210 of this chapter, including labeling.

(ii) It is also intended for use in the prevention of those infections of chickens specified in subparagraph (6) of this paragraph; it contains amprolium in the amount and under the conditions specified in subdivision (i) of this subparagraph; and it contains, per ton of feed, not less than 50 grams and not more than 100 grams of chlortetracycline.

(iii) It is also intended for use in the treatment of those infections of chickens specified in subparagraph (7) of this paragraph; it contains amprolium in the amount and under the conditions set forth in subdivision (i) of this subparagraph; and it contains, per ton of feed, not less than 100 grams and not more than 200 grams of chlortetracycline, or 75 grams of streptomycin and 15 grams of penicillin.

(iv) It is also intended for use in the prevention of those infections of chickens specified in subparagraph (9) of this

paragraph; it contains amprolium in the amount and under the conditions specified in subdivision (i) of this subparagraph; and it contains, per ton of feed, not less than 50 grams and not more than 100 grams of bacitracin (as feed grade bacitracin, bacitracin methylene disalicylate, or feed grade zinc bacitracin).

(v) It is also intended for use in the treatment of those infections of chickens specified in subparagraph (10) of this paragraph; it contains amprolium in the amount and under the conditions set forth in subdivision (i) of this subparagraph; and it contains, per ton of feed, not less than 100 grams and not more than 200 grams of bacitracin (as feed grade bacitracin, bacitracin methylene disalicylate, or feed grade zinc bacitracin).

(vi) It is also intended for use in the treatment of infectious sinusitis, blue comb (nonspecific infectious enteritis, mud fever), and hexamitiasis in turkeys; it contains amprolium in the amount and under the conditions specified in subdivision (i) (*a*) (*1*) of this subparagraph; and it contains, per ton of feed, a combination of 75 grams of streptomycin and 15 grams of penicillin.

(45) It is a medicated chicken or turkey feed containing antibiotics and zoalene in the amounts and for the purposes indicated in § 121.207 of this chapter; *Provided, however,* That such medicated complete feed has been prepared from a concentrated zoalene-antibiotic medicated feed that contained not more than 0.0375 percent zoalene. If the complete medicated feed is prepared from a product of zoalene that contains more than 0.0375 percent zoalene, it is exempt from certification only under the condition that there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition or labeling of such drug, or the methods used in and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtains the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner. Both concentrates and finished poultry feed containing zoalene must comply with all the requirements of § 121.207 of this chapter, including labeling.

(46) It is intended for use as an aid in improving pelt size, improving growth rate, and improving feed efficiency of mink; its labeling contains adequate directions and warnings for such use; and it contains not less than 20 grams nor more than 50 grams of chlortetracycline per ton of complete feed.

(47) It is intended for use solely as an aid in improving growth and feed efficiency in pheasants; its labeling bears adequate directions and warnings for such use; and it contains, per ton of complete ration, the following quantities of antibiotics:

(i) Bacitracin (as feed grade bacitracin, bacitracin methylene disalicylate, or feed grade zinc bacitracin): Not less than 4 grams and not more than 50 grams; or

(ii) Penicillin: Not less than 2.4 grams and not more than 50 grams.

(48) It is intended for use solely as an an aid in stimulating growth in quail chicks up to 5 weeks of age; its labeling bears adequate directions and warnings for such use; and it contains, per ton of complete feed, the following quantities of antibiotics:

(i) Bacitracin: Not less than 5 grams and not more than 20 grams; or

(ii) Penicillin: Not less than 5 grams and not more than 20 grams.

(49) It is a medicated chicken or turkey feed containing antibiotics and reserpine in the amounts and for the purposes indicated in § 121.205 of this chapter; its labeling bears adequate directions and warnings for such use; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition of such drug, or the methods used in, and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner.

(50) It is a medicated chicken feed containing antibiotics and hygromycin B in the amounts and for the purposes indicated in § 121.213 of this chapter; or if it is hygromycin B concentrate, it contains not more than 16,000 units (16 milligrams) of hygromycin B per pound; its labeling bears adequate directions and warnings for such use; and there has been submitted to the Commissioner, in triplicate, adequate information of the kind described in § 146.7 to establish the safety and efficacy of the article and to guarantee its identity, strength, quality, and purity. The exemption shall expire at the beginning of any act changing the composition of such drug, or the methods used in, and the facilities and controls used for its manufacturing, processing, and packaging, or in its labeling, unless the person who obtained the exemption has submitted to the Commissioner, in triplicate, amended information that describes such proposed changes, and such amendment has been accepted by the Commissioner.

(51) It is a medicated chicken and turkey feed containing bacitracin or zinc bacitracin up to 500 grams per ton or up to 500 grams per ton of a combination of either with penicillin in the amounts and for the purposes indicated in §§ 121.232 and 121.233 of this chapter and its labeling bears adequate directions and warnings for such use.

(52) It is a cattle feed containing zinc bacitracin in the amounts and for the purposes indicated in § 121.225 of this chapter and its labeling bears adequate directions and warnings for such use.

(c) [Reserved.]

(d) Fees: The fees for the services rendered with respect to each application for an exemption from certification under the regulations in paragraph (b) of this section, and for each amendment thereto, shall be:

(1) $5.00 for each medicated feed formula containing one or more new-drug substances described in an initial application.

(2) $5.00 for changes in one or more new-drug substances contained in a medicated feed formula described in an amendment to such application.

The fee prescribed by this paragraph shall accompany each application and each amendment to such application unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d).

(53) It is a medicated feed for turkeys and contains chlortetracycline hydrochloride and dietary calcium in the amounts and for the purposes indicated in § 121.208(d), Table 1, Item 12, of this chapter; and its labeling bears adequate directions and warnings for such use.

§ 146.27 Antibiotics for fish diseases.

Any antibiotic drug subject to the regulations in this chapter intended for use solely in the prevention or treatment of disease in fish and conspicuously so labeled shall be exempt from the requirements of sections 502(1) and 507 of the act if the fish so treated are not intended for human consumption.

(Interprets or applies secs. 502, 52 Stat. 1050, 59 Stat. 463, as amended; 21 U.S.C. 352)

§ 146.28 Antibiotics for bull semen.

Any certifiable antibiotic drug subject to the regulations in this chapter intended for use solely as a preservative for bull semen, and conspicuously so labeled, shall be exempt from the requirements of sections 502 (l) and 507 of the act.

§ 146.29 Biological drugs that contain antibiotics.

Biological drugs that contain any certifiable antibiotic drug subject to the regulations in this chapter, and the purpose of the antibiotic is for use only as a preservative and the biological drug is conspicuously so labeled, shall be exempt from the requirements of sections

502(l) and 507 of the act, if such drugs are licensed under the Public Health Service Act of July 1, 1944 (58 Stat. 682; 42 U.S.C. 201 et seq.) or under the Virus-Serum-Toxin Act of March 4, 1913 (37 Stat. 832; 21 U.S.C. 151 et seq.)

§ 146.30 Exemption for the salts of antibiotic drugs for use in teaching, law enforcement, research, and analysis.

The salts of antibiotic drugs subject to section 507 of the act shall be exempt from the requirements of section 502 (*l*) if shipped or sold to, or in the possession of, persons regularly and lawfully engaged in instruction in pharmacy, chemistry, or medicine not involving clinical use; or in law enforcement; or in research not involving clinical use; or in chemical analysis or physical testing, provided they are to be used only for such instruction, law enforcement, research, analysis, or testing, and provided further that their labels bear the statement "Not for drug use."

PART 146a—CERTIFICATION OF PENICILLIN AND PENICILLIN-CONTAINING DRUGS

Sec.
146a.11 Buffered methicillin sodium (buffered sodium-2,6-dimethoxyphenyl penicillin).
146a.12 Sodium oxacillin.
146a.13 Sodium oxacillin tablets.
146a.14 Sodium oxacillin capsules.
146a.15 Methicillin sodium.
146a.16 Phenethicillin potassium (potassium *a*-phenoxyethyl penicillin).
146a.17 Phenethicillin potassium (potassium *a*-phenoxyethyl penicillin) tablets.
146a.18 Phenethicillin potassium (potassium *a*-phenoxyethyl penicillin) for oral solution.
146a.19 Benzathine penicillin V for aqueous injection veterinary.
146a.20 Penicillin-streptomycin-bacitracin methylene disalicylate-neomycin ointment; penicillin-dihydrostreptomycin-bacitracin methylene disalicylate-neomycin ointment.
146a.21 Capsules penicillin - tetracycline phosphate complex-novobiocin-nystatin veterinary.
146a.22 Penicillin-streptomycin-neomycin-polymyxin ointment; penicillin dihydrostreptomycin-neomycin-polymyxin ointment.
146a.23 Penicillin - streptomycin - erythromycin ointment; penicillin-dihydrostreptomycin - erythromycin ointment.
146a.24 Sodium penicillin (penicillin sodium, penicillin sodium salt), calcium penicillin (penicillin calcium, penicillin calcium salt), crystalline penicillin (crystalline penicillin sodium, crystalline penicillin sodium salt, crystalline penicillin potassium, crystalline penicillin potassium salt, crystalline penicillin G sodium, crystalline penicillin G sodium salt, crystalline penicillin G potassium, crystalline penicillin G potassium salt, crystalline penicillin O sodium, crystalline penicillin O sodium salt, crystalline penicillin O potassium, crystalline penicillin O potassium salt).
146a.25 Penicillin in oil and wax. (Calcium penicillin in oil and wax, crystalline penicillin in oil and wax).
146a.26 Penicillin ointment.
146a.27 Penicillin tablets.
146a.28 Crystalline penicillin G oral suspension, crystalline penicillin G sodium oral suspension, potassium penicillin G oral suspension.
146a.29 Penicillin with aluminum hydroxide gel.
146a.30 Penicillin troches.
146a.31 Penicillin dental cones (calcium penicillin dental cones, penicillin dental cones calcium salt, crystalline penicillin dental cones).
146a.32 Penicillin with vasoconstrictor; penicillin with —— (the blank being filled in with the common or usual name of the vasoconstrictor).
146a.33 Penicillin for surface application.
146a.34 Tablets aluminum penicillin.
146a.35 Penicillin sulfonamide powder (calcium penicillin sulfonamide powder, crystalline penicillin sulfonamide powder).
146a.36 Penicillin vaginal suppositories.
146a.37 Buffered crystalline penicillin.
146a.38 Capsules buffered penicillin with pectin hydrolysate (capsules buffered potassium penicillin with pectin hydrolysate).
146a.39 Capsules procaine penicillin in oil.
146a.40 Penicillin bougies (sodium penicillin bougies, calcium penicillin bougies, potassium penicillin bougies, procaine penicillin bougies, penicillin bougies sodium salt, penicillin bougies calcium salt, penicillin bougies potassium salt, penicillin bougies procaine salt).
146a.41 Crystalline penicillin and epinephrine in oil.
146a.42 Aluminum penicillin (aluminum penicillin salt).
146a.43 Aluminum penicillin in oil.
146a.44 Procaine penicillin (penicillin procaine salt), procaine penicillin G (penicillin G procaine salt).
146a.45 Procaine penicillin in oil.
146a.46 Crystalline penicillin for inhalation therapy.
146a.47 Procaine penicillin for aqueous injection.
146a.48 Ephedrine penicillin (penicillin ephedrine salt), ephedrine penicillin G (penicillin G ephedrine salt).
146a.49 Ephedrine penicillin tablets.
146a.50 Procaine penicillin and buffered crystalline penicillin for aqueous injection.
146a.51 Buffered penicillin powder, penicillin powder with buffered aqueous diluent.
146a.52 Procaine penicillin and crystalline penicillin in oil.
146a.53 Capsules penicillin and novobiocin.
146a.54 Penicillin-streptomycin ointment (penicillin-streptomycin mineral oil suspension); penicillin-dihydrostreptomycin ointment (penicillin -dihydrostreptomycin mineral oil suspension).
146a.55 Penicillin-streptomycin bougies; penicillin - dihydrostreptomycin bougies.
146a.56 Penicillin-bacitracin ointment.
146a.57 Procaine penicillin and streptomycin in oil; procaine penicillin and dihydrostreptomycin in oil.
146a.58 Penicillin-streptomycin; penicillin-dihydrostreptomycin veterinary.
146a.59 Penicillin tooth powder (tooth powder with penicillin).
146a.60 Penicillin-bacitracin troches; penicillin-zinc bacitracin troches.
146a.61 Potassium penicillin V (potassium penicillin V salt).
146a.62 Penicillin-neomycin ointment.
146a.63 Crystalline penicillin and bacitracin.
146a.64 *l*-Ephenamine penicillin G (penicillin G *l*-ephenamine salt).
146a.65 *l*-Ephenamine penicillin G in oil.
146a.66 *l*-Ephenamine penicillin G for aqueous injection.
146a.67 Procaine penicillin in streptomycin sulfate solution; procaine penicillin in dihydrostreptomycin sulfate solution veterinary (procaine penicillin in crystalline dihydrostreptomycin sulfate solution veterinary).
146a.68 Benzathine penicillin G (benzathine penicillin G salt).
146a.69 Benzathine penicillin G oral suspension, benzathine penicillin G for oral suspension (benzathine penicillin G powder).
146a.70 Penicillin-streptomycin-bacitracin ointment; penicillin - dihydrostreptomycin - bacitracin ointment; penicillin-streptomycin-bacitracin methylene disalicylate ointment; penicillin - dihydrostreptomycin-bacitracin methylene disalicylate ointment.
146a.71 Penicillin-streptomycin dental cones; penicillin-dihydrostreptomycin dental cones.
146a.72 Hydrabamine penicillin V (penicillin V hydrabamine salt).
146a.73 Hydrabamine penicillin V oral suspension.
146a.74 Diethylaminoethyl ester penicillin G hydriodide (penicillin G diethylaminoethyl ester hydriodide).
146a.75 Diethylaminoethyl ester penicillin G hydriodide for aqueous injection (penicillin G diethylaminoethyl ester hydriodide for aqueous injection).
146a.76 Penicillin-streptomycin implantation pellets; penicillin-dihydrostreptomycin implantation pellets.
146a.77 Benzathine penicillin G for aqueous injection.
146a.78 Benzathine penicillin G and buffered crystalline penicillin for aqueous injection.
146a.79 Chloroprocaine penicillin O (penicillin O chloroprocaine salt).

Sec.
146a.80 Chloroprocaine penicillin O for aqueous injection.
146a.81 Penicillin-streptomycin vaginal suppositories; penicillin-dihydrostreptomycin vaginal suppositories.
146a.82 Penicillin-streptomycin-bacitracin dental paste; penicillin-dihydrostreptomycin-bacitracin dental paste.
146a.83 Procaine penicillin-streptomycin-neomycin-erythromycin in oil; procaine penicillin-dihydrostreptomycin-neomycin-erthyromycin in oil.
146a.84 Penicillin and dihydrostreptomycin-streptomycin sulfates veterinary; procaine penicillin in dihydrostreptomycin-streptomycin sulfates solution veterinary.
146a.85 Benzathine-procaine-buffered crystalline penicillins for aqueous injection.
146a.86 Benzathine penicillin G and procaine penicillin for aqueous injection.
146a.87 Penicillin-bacitracin-neomycin ointment; penicillin-bacitracin-neomycin in oil.
146a.88 Penicillin-streptomycin tablets; penicillin-dihydrostreptomycin tablets.
146a.89 Penicillin-streptomycin-neomycin in oil; penicillin-dihydrostreptomycin-neomycin in oil; penicillin-streptomycin-neomycin ointment; penicillin-dihydrostreptomycin-neomycin ointment.
146a.90 Procaine penicillin and benzathine penicillin G in streptomycin sulfate solution; procaine penicillin and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (procaine penicillin and benzathine penicillin G in crystaline dihydrostreptomycin sulfate solution veterinary).
146a.91 Benzathine penicillin G and streptomycin; benzathine penicillin G and dihydrostreptomycin veterinary.
146a.92 Tablets benzathine penicillin G and crystalline penicillin.
146a.93 Penicillin-streptomycin powder; penicillin-dihydrostreptomycin powder.
146a.94 Dibenzylamine penicillin G (dibenzylamine penicillin G salt).
146a.95 Dibenzylamine penicillin and potassium penicillin powder, buffered.
146a.96 Dibenzylamine penicillin and streptomycin in oil; dibenzylamine penicillin and dihydrostreptomycin in oil.
146a.97 Hydrabamine penicillin G (hydrabamine penicillin G salt).
146a.98 Hydrabamine penicillin G oral suspension.
146a.99 Capsules crystalline penicillin G (capsules crystalline penicillin G potassium, capsules crystalline penicillin G sodium).
146a.100 Benzathine penicillin G in oil.
146a.101 Benzathine penicillin G and procaine penicillin G in oil.
146a.102 Benzathine penicillin G-procaine penicillin G-streptomycin in oil; benzathine penicillin G-procaine penicillin G-dihydrostreptomycin in oil veterinary.
146a.103 Penicillin V (phenoxymethyl penicillin).
146a.104 Penicillin V for oral suspension (phenoxymethyl penicillin for oral suspension); potassium penicillin V for oral solution.
Sec.
146a.105 Benzathine penicillin V (benzathine penicillin V salt).
146a.106 Tablets benzathine penicillin G and penicillin V.
146a.107 Capsules penicillin V.
146a.108 Procaine penicillin-streptomycin-polymyxin in oil; procaine penicillin - dihydrostreptomycin - polymyxin in oil; procaine penicillin - streptomycin - polymyxin ointment; procaine penicillin-dihydrostreptomycin-polymyxin ointment.
146a.109 Benzathine penicillin V oral suspension; benzathine penicillin V for oral suspension.
146a.110 Benzathine penicillin G in streptomycin sulfate solution; benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).
146a.111 Procaine penicillin - neomycin-polymyxin in oil; procaine penicillin-neomycin-polymyxin ointment.
146a.112 Crystalline penicillin-streptomycin-polymyxin - oxytetracycline-carbomycin powder veterinary; crystalline penicillin - dihydrostreptomycin - polymyxin - oxytetracycline-carbomycin powder veterinary.

AUTHORITY: §§ 146a.24 to 146a.112 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 146a.11 Buffered methicillin sodium (buffered sodium-2,6-dimethoxyphenyl penicillin).

(a) *Standards of identity, strength, quality, and purity.* Buffered methicillin sodium conforms to all the requirements and is subject to all procedures prescribed by § 146a.15(a) for methicillin sodium, except that:

(1) It contains the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids; such sodium citrate conforms to the standards prescribed therefor by the U.S.P.

(2) It may contain one or more suitable preservatives.

(3) The methicillin content is corrected for the sodium citrate content.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless, transparent glass. Each such container shall contain 1 gram, 2 grams, 3 grams, 4 grams, 5 grams, or 6 grams.

(c) *Labeling*—(1) *If it is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified: *Provided, however,* That such expiration date may be omitted from the immediate container if it contains a single dose and it is packaged in an individual wrapper or container.

(ii) On the circular or other labeling within or attached to the package, the statement, "Reconstituted solutions may be stored for not more than 24 hours at room temperature and not more than 4 days under refrigeration."

(2) *If it is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The number of micrograms of the free acid of methicillin per milligram and the number of grams or kilograms in the immediate container.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(d) *Request for certification, check tests, and assays; samples.* Proceed as directed in § 146a.15(d), except that a person who requests certification of a batch shall also submit with his request a statement showing the quantity of sodium citrate used in making the batch and that such sodium citrate conforms to the requirements prescribed therefor by this section. In case of an initial request for certification. he shall submit an accurately representative sample of such sodium citrate consisting of approximately 5 grams.

(e) *Fee.* In addition to the fees prescribed in § 146a.15(e) the fee for the services rendered with respect to the sample of sodium citrate submitted as prescribed in paragraph (d) of this section shall be $4.00.

§ 146a.12 Sodium oxacillin.

(a) *Standards of identity, strength, quality, and purity.* Sodium oxacillin is the crystalline monohydrated sodium salt of 5-methyl-3-phenyl-4-isoxazolyl penicillin. It is so purified and dried that:

(1) It contains not less than 815 micrograms of the free acid of oxacillin per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 6.0 percent.

(4) Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 4.5 and not more than 7.5.

(5) Its sodium oxacillin content is not less than 90 percent.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except

that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of micrograms per milligram and the number of grams in the immediate container.

(3) The statement "Expiration date ----------," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(4) The statement "For use in the manufacture of nonparenteral drugs only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him of the batch for potency, toxicity, moisture, pH, sodium oxacillin content, crystallinity, and identity.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of nine packages, each containing approximately 300 milligrams plus one package containing approximately 2 grams, taken from a different part of the batch, packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $5.00 for each immediate container in the sample submitted in accordance with paragraph (d)(2) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.13 Sodium oxacillin tablets.

(a) *Standards of identity, strength, quality, and purity.* Sodium oxacillin tablets are tablets composed of sodium oxacillin, with or without one or more suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings. The potency of each tablet is not less than 250 milligrams. Its moisture content is not more than 6.0 percent. Tablets not exceeding 15 millimeters in diameter or not intended only for preparing solutions shall disintegrate within 1 hour. The sodium oxacillin conforms to the requirements of § 146a.12(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each sodium oxacillin tablet is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U.S.P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106 (b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(2) If the batch contains buffer substances, the name of each such substance used in making the batch.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of sodium oxacillin tablets shall submit with his request a statement showing the batch mark, the number of tablets in such batch, the number of tablets of the batch packaged into dispensing-size containers during each day's packaging operations, the batch mark (and unless it was previously submitted) the date on which the latest assay of the sodium oxacillin used in making such batch was completed, the number of milligrams in each tablet, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed, average moisture of tablets collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) The sodium oxacillin used in making the batch: Potency, content of sodium oxacillin, toxicity, moisture, pH, crystallinity, and identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For potency and moisture:

(*1*) If the person who requests certification is the manufacturer of the batch: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets, collected by taking single tablets at such intervals throughout the entire time of tableting the batch that the quantities tableted during the intervals are approximately equal;

(*2*) If, after tableting, such person packages the batch into dispensing-size containers: 20 tablets collected at equal intervals during each day the tablets are being packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed; or

(*3*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of tablets filled by such person into dispensing-size containers during each day's packaging operations): One tablet for each 5,000 tablets, but in no case less than 30 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets that the quantities packaged during the intervals are approximately equal.

(*b*) For disintegration time: 6 tablets.

(ii) The sodium oxacillin used in making the batch: 10 packages, each containing not less than 300 milligrams, packaged in accordance with the requirements of § 146a.12(b).

(iii) In case of an initial request for certification, each other substance used in making the batch: One package of each, containing approximately 5 grams.

(4) The result referred to in subparagraph (2)(ii) of this paragraph and the sample referred to in subparagraph (3)(ii) of this paragraph are not required if such result and sample have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch of tablets under the regulations in this section shall be:

(1) $0.75 for each tablet in the samples submitted in accordance with paragraph (d)(3)(i)(*a*) (*1*) and (*3*) of this section; $3.00 for the samples submitted in accordance with paragraph (d)(3)(i)

(a)(2) and (b) of this section; $5.00 for each package in the sample submitted in accordance with paragraph (d)(3)(ii) of this section; $4.00 for each package in the sample submitted in accordance with paragraph (d)(3)(iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such tablets and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.14 Sodium oxacillin capsules.

(a) *Standards of identity, strength, quality, and purity.* Sodium oxacillin capsules are capsules composed of sodium oxacillin, with or without one or more buffer substances, diluents, binders, lubricants, vegetable oils, colorings, and flavorings, enclosed in a gelatin capsule. The potency of each capsule is not less than 250 milligrams. The moisture content is not more than 6 percent. The sodium oxacillin conforms to the requirements of § 146a.12. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees.* Sodium oxacillin capsules conform to all requirements and procedures prescribed for sodium oxacillin tablets by § 146a.13 (b), (c), (d), and (e), except with respect to disintegration time.

§ 146a.15 Methicillin sodium.

(a) *Standards of identity, strength, quality, and purity.* Methicillin sodium is the crystalline monohydrated sodium salt of 2,6-dimethoxyphenyl penicillin. It is so purified and dried that:

(1) It contains not less than 815 micrograms of the free acid of methicillin per milligram.

(2) It is sterile.

(3) It is nonpyrogenic.

(4) It is nontoxic.

(5) Its moisture content is not more than 6.0 percent.

(6) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(7) Its methicillin content is not less than 90 percent.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless transparent glass. Each such container shall contain 1 gram.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) On the circular or other labeling within or attached to the package, a statement that solutions prepared from the drug should be stored under refrigeration and used within 24 hours.

(2) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container, the following:

(i) The number of micrograms of the free acid of methicillin per milligram, and the number of grams or kilograms in the immediate container.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of milligrams in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH, methicillin content, crystallinity, and identity.

(2) If such batch is packaged for dispensing, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility: One immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(ii) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals through the entire time of packing the batch that the quantities packaged during the intervals are approximately equal.

(3) If such batch is packaged for repacking or for use as an ingredient in the manufacture of another drug, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility: Nine packages, each containing approximately 300 milligrams, plus one package containing approximately 2 grams.

(ii) For sterility testing: 10 packages, each containing approximately 300 milligrams.

Each such package shall be packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $5.00 for each immediate container in the samples submitted in accordance with paragraph (d)(2)(i) and (3)(i) of this section; $10.00 for all containers submitted in accordance with paragraph (d)(2)(ii) or (3)(ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.16 Phenethicillin potassium (potassium α-phenoxyethyl penicillin).

(a) *Standards of identity, strength, quality, and purity.* Phenethicillin potassium is the crystalline DL-α-phenoxyethyl, penicillin potassium salt. It contains not less than 90 percent by weight of phenethicillin potassium. It contains not less than 55 percent and not more than 75 percent of L-α-phenoxyethyl penicillin potassium. It is so purified and dried that:

(1) Its potency is not less than 1,328 units per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 1.5 percent.

(4) Its pH in an aqueous solution of 5,000 units to 10,000 units per milliliter is not less than 4.0 and not more than 7.5.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of units per milligram and the number of grams in the immediate container.

(3) The statement "Expiration date _____," the blank being filled in with the

date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 30 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(4) The statement "For use in the manufacture of nonparenteral drugs only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, content of phenethicillin potassium, content of L-α-phenoxyethyl penicillin potassium, toxicity, moisture, pH, crystallinity, and identity.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of 10 packages, each containing approximately 300 milligrams taken from a different part of such batch, packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $5.00 for each immediate container in the sample submitted in accordance with paragraph (d)(2) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.17 Phenethicillin potassium (potassium α-phenoxyethyl penicillin) tablets.

(a) *Standards of identity, strength, quality, and purity.* Phenethicillin potassium tablets are tablets composed of phenethicillin potassium, with or without one or more suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings, and with or without one or more suitable analgesic substances, antihistaminics, and vasoconstrictors. The potency of each tablet is not less than 50,000 units, and if it is less than 100,000 units it is unscored. Its moisture content is not more than 1.5 percent unless the person who requests certification has submitted to the Commissioner information adequate to prove that his drug is stable when it has a moisture content exceeding this amount. In no case shall its moisture content exceed 2.0 percent. Tablets not exceeding 15 millimeters in diameter or not intended only for preparing solutions shall disintegrate within 1 hour. The phenethicillin potassium conforms to the requirements of § 146a.16(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed by such official compendium.

(b) *Packaging.* Unless each phenethicillin potassium tablet is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U.S.P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) If the batch contains buffer substances, the name of each such substance.

(ii) The statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, 30 months, or 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) On the label and labeling, if it contains, in addition to phenethicillin potassium, one or more of the active ingredients specified in paragraph (a) of this section, after the name "phenethicillin potassium tablets," wherever it appears, the words "with _____," the blank being filled in with the common or usual name of each other ingredient, in juxtaposition with such name.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of phenethicillin potassium tablets shall submit with his request a statement showing the batch mark, the number of tablets in such batch, the number of tablets of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each tablet, the date on which the latest assay of the drug comprising such batch was completed, the date (unless submitted previously) on which the latest assay of the phenethicillin potassium used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed, average moisture of tablets collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) The phenethicillin potassium used in making the batch: Potency, content of phenethicillin potassium, content of L-α-phenoxyethyl, penicillin potassium, toxicity, moisture, pH, crystallinity, and identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For potency and moisture:

(*1*) If the person who requests certification is the manufacturer of the batch: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets collected by taking single tablets at such intervals throughout the entire time of tableting the batch that the quantities tableted during the intervals are approximately equal;

(*2*) If, after tableting, such person packages the batch into dispensing-size containers: 20 tablets collected at equal intervals during each day the tablets are being packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed; or

(*3*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of tablets filled by such person into dispensing-size

containers during each day's packaging operations): One tablet for each 5,000 tablets, but in no case less than 30 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets that the quantities packaged during the intervals are approximately equal.

(*b*) For disintegration time: 6 tablets.

(ii) The phenethicillin potassium used in making the batch: 10 packages, each containing not less than 300 milligrams, packaged in accordance with the requirements of § 146a.16(b).

(iii) In case of an initial request for certification, each other substance used in making the batch: One package of each, containing approximately 5 grams.

(4) The result referred to in subparagraph (2) (ii) of this paragraph and the sample referred to in subparagraph (3) (ii) of this paragraph are not required if such result and sample have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch of phenethicillin potassium under the regulations in this section shall be:

(1) $0.75 for each tablet in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) (*1*) and (3) of this section; $3.00 for the sample submitted in accordance with paragraph (d) (3) (i) (*a*) (*2*) and (*b*) of this section; $5.00 for each package in the sample submitted in accordance with paragraph (d) (3) (ii) of this section; $4.00 for each package in the sample submitted in accordance with paragraph (d) (3) (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such tablets and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.18 Phenethicillin potassium (potassium *a*-phenoxyethyl penicillin) for oral solution.

(a) *Standards of identity, strength, quality, and purity.* Phenethicillin potassium for oral solution is a mixture of phenethicillin potassium, with or without one or more suitable and harmless colorings, flavorings, buffer substances, and preservatives, and with or without one or more suitable analgesic substances, antihistaminics, and vasoconstrictors. Its moisture content is not more than 1.0 percent. The phenethicillin potassium used conforms to the requirements of § 146a.16(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container of phenethicillin potassium for oral solution shall be a tight container as defined by the U.S.P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) If the batch contains buffer substances, the name of each such substance.

(ii) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, or 30 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) On the label and labeling, if it contains, in addition to phenethicillin potassium, one or more of the active ingredients specified in paragraph (a) of this section, after the name "phenethicillin potassium for oral solution," wherever it appears, the words "with ----------," the blank being filled in with the common or usual name of each other ingredient, in juxtaposition with such name.

(d) (1) *Request for certification; samples.* In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of phenethicillin potassium for oral solution shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark, and (unless it was previously submitted) the date on which the latest assay of the phenethicillin potassium used in making such batch was completed, the number of units in each immediate container, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The phenethicillin potassium used in making the batch: Potency, content of phenethicillin potassium, content of L-*a*-phenoxyethyl, penicillin potassium, toxicity, moisture, pH, crystallinity, and identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The phenethicillin potassium used in making the batch: 10 packages containing not less than 300 milligrams packaged in accordance with the requirements of § 146a.16(b).

(iii) In the case of an initial request for certification, each other substance used in making the batch: One package of each containing approximately 5 grams.

(4) The result referred to in subparagraph (2) (ii) of this paragraph and the sample referred to in subparagraph (3) (ii) of this paragraph are not required if such result and sample have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch of phenethicillin potassium for oral suspension under the regulations in this section shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) and (iii) of this section: $5.00 for each package of the sample submitted in accordance with paragraph (d) (3) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8 of this chapter.

§ 146a.19 Benzathine penicillin V for aqueous injection veterinary.

(a) *Standards of identity, strength, quality, and purity.* Benzathine penicillin V for aqueous injection is a dry mixture of benzathine penicillin V and one or more suitable and harmless suspending or dispersing agents and with or without one or more suitable and harmless preservatives, buffer substances, and local anesthetics; or it is an aqueous suspension of benzathine penicillin V and one or more suitable and harmless suspending or dispersing agents, buffer substances, and preservatives, and with or without one or more suitable and harmless local anesthetics. It is so purified that:

(1) If it is an aqueous suspension of the drug, each container or each milliliter shall contain not less than 300,000 units.

(2) It is sterile.

(3) It is nonpyrogenic.

(4) It is nontoxic.

(5) If it is the dry mixture of the drug, its moisture content is not more than 8 percent.

(6) Its pH in saturated solution is not less than 5.0 and not more than 7.5.

The benzathine penicillin V used conforms to the requirements of § 146a.105 (a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U.S.P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container shall contain not less than 3,000,000 units and each may be packaged in combination with a container of a suitable aqueous diluent.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(c) of this chapter (regulations issued under section 502(f) of the act), each package shall bear, on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The statement "Expiration date ----------," the blank being filled in, if it is a dry mixture of the drug, with the date that is 24 months, or if it is the aqueous suspension of the drug, with the date that is 12 months, after the month during which the batch was certified.

(ii) The statement "For veterinary use only."

(iii) The statement "*Warning*—Not for use in animals producing milk, since this use will result in contamination of the milk.

(2) On the outside wrapper or container, if it is the aqueous suspension of the drug, the statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)," unless the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him complies with the standards prescribed in paragraph (a) of this section after having been stored at room temperature.

(3) On a circular or other labeling within or attached to the package of the dry mixture of the drug, the conditions under which a suspension made from such drug should be stored, and the statement "Sterile suspension may be kept at room temperature for 1 week, or in refrigerator for 3 weeks, without significant loss of potency."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of benzathine penicillin V for aqueous injection veterinary shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the benzathine penicillin V used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section. If such batch, or any part thereof, is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following:

(i) The batch: Potency, sterility, moisture (unless it is an aqueous suspension of the drug), pyrogens, toxicity, pH.

(ii) The benzathine penicillin V used in making the batch: Potency, penicillin V content, crystallinity.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: One immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The benzathine penicillin V used in making the batch: Three packages containing approximately equal portions of not less than 500 milligrams each, packaged in accordance with the requirements of § 146a.105(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each, containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch of benzathine penicillin V for aqueous injection that is to be packaged in combination with an aqueous diluent that is not recognized by the U.S.P., or when any change is made in the composition of such diluent: 5 packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility: 10 packages.

(ii) For sterility testing: 10 packages.

Each such package shall contain not less than approximately 300 milligrams taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) The result referred to in subparagraph (2)(ii) of this paragraph and the sample referred to in subparagraph (3)(ii) of this paragraph are not required if such result or sample has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d)(3)(i)(*a*), (ii), (iii), (iv), and (4)(i) of this section; $10.00 for all containers submitted in accordance with paragraph (d)(3)(i)(*b*) and (4)(ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.20 Penicillin-streptomycin-bacitracin methylene disalicylate-neomycin ointment; penicillin-dihydrostreptomycin-bacitracin methylene disalicylate-neomycin ointment.

Penicillin - streptomycin - bacitracin methylene disalicylate-neomycin ointment and penicillin-dihydrostreptomycin-bacitracin methylene disalicylate-neomycin ointment conform to all requirements prescribed by § 146a.70 for penicillin-streptomycin-bacitracin methylene disalicylate ointment and penicillin - dihydrostreptomycin - bacitracin methylene disalicylate ointment, except that:

(a) Each dose, as recommended in its labeling, shall contain the equivalent of not less than 2,000 units of bacitracin and not less than 100 milligrams of neomycin. The neomycin used conforms to the standards prescribed by § 146e.410(a) of this chapter, except the standard for toxicity.

(b) In addition to complying with the requirements of § 146a.70(a)(3), a person who requests certification of a batch shall submit with his request a statement showing the batch marks and (unless it was previously submitted) the results and date of the latest tests and

assays of the neomycin used in making the batch for potency, moisture, and pH. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages of the neomycin used in making the ointment, containing approximately equal portions of 0.5 gram each.

(c) The fees for the services rendered with respect to the sample submitted in accordance with paragraph (b) of this section shall be $4.00 for each immediate container of the neomycin used in making the ointment.

§ 146a.21 Capsules penicillin-tetracycline phosphate complex-novobiocin-nystatin veterinary.

(a) *Standards of identity, strength, quality, and purity.* Capsules penicillin-tetracycline phosphate complex-novobiocin-nystatin veterinary are crystalline potassium penicillin G, tetracycline phosphate complex, monosodium novobiocin, and nystatin, with or without one or more suitable and harmless buffer substances, lubricants, colorings, and flavorings, enclosed in a suitable and harmless gelatin capsule. Each capsule contains 100,000 units of penicillin, the equivalent of 50 milligrams of tetracycline hydrochloride as the phosphate complex, 50 milligrams of novobiocin, and 50,000 units of nystatin. The moisture content is not more than 8 percent. The crystalline penicillin G potassium used conforms to the requirements of § 146a.24(a), except § 146a.24(a) (2) and (4). The tetracycline phosphate complex used conforms to the requirements of § 146c.232(a) of this chapter. The crystalline monosodium used conforms to the standards prescribed by § 146a.53 (a). The nystatin used conforms to the standards prescribed by § 146c.224(a) of this chapter. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. and shall be of such composition that they will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of units of penicillin, the number of milligrams of tetracycline phosphate complex expressed in its equivalency of tetracycline hydrochloride, the number of milligrams of novobiocin, and the number of units of nystatin in each capsule of the batch.

(iii) The name of each buffer substance used in making the batch.

(iv) The statement "Expiration date ----------," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(v) The statement, "For oral veterinary use only in the treatment of susceptible bacterial infections in dogs and cats."

(2) On a circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary use of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark; the number of capsules in such batch; the number of capsules of the batch packaged into dispensing-size containers during each day's packaging operations; the batch marks and (unless submitted previously) the dates on which the latest assays of the penicillin, tetracycline phosphate complex, novobiocin, and nystatin used in making such batch were completed; the quantity of each ingredient used in making the batch; the date on which the latest assay of the drug comprising such batch was completed; and a statement that each other ingredient used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency and average moisture of capsules collected during the time of capsuling the batch, and, unless the capsules are packaged into dispensing-size containers immediately after they are capsuled, average moisture of capsules collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency and average moisture of capsules collected during each day the capsules are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch: Potency, toxicity, moisture, pH, crystallinity, and heat stability.

(iii) The tetracycline phosphate complex used in making the batch: Potency, toxicity, moisture, pH, crystallinity, absorptivity, and identity.

(iv) The novobiocin used in making the batch: Potency, toxicity, pH, moisture, and crystallinity.

(v) The nystatin used in making the batch: Potency, toxicity, pH, moisture, and identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request accurately representative samples of the following:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: One capsule for each 5,000 capsules in the batch, but in no case less than 30 capsules collected by taking single capsules at such intervals throughout the entire time of capsuling the batch that the quantities capsuled during the intervals are approximately equal;

(*b*) If, after capsuling, such person packages the batch into dispensing-size containers: 20 capsules collected at equal intervals during each day the capsules are being packaged, except that this sample is not required if the capsules are packaged immediately after they are capsuled; or

(*c*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of capsules filled by such person into dispensing-size containers during each day's packaging operations): One capsule for each 5,000 capsules, but in no case less than 30 capsules collected by taking single capsules at such intervals throughout each day of packaging the capsules that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146a.24 (b).

(iii) The tetracycline phosphate complex used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, plus one package containing approximately 1 gram. Each such package shall be packaged in accordance with the requirements of § 146c.232 (b) of this chapter.

(iv) The novobiocin used in making the batch: 10 packages, each containing approximately equal portions of not less than 300 milligrams.

(v) The nystatin used in making the batch: 10 packages, each containing approximately equal portions of not less than 300 milligrams.

(vi) In case of an initial request for certification, each other ingredient used in making the batch: One package of each, containing approximately 5 grams.

(4) The results referred to in subparagraph (2) (ii), (iii), (iv), and (v) of this paragraph and the samples referred to in subparagraph (3) (ii), (iii), (iv), and (v) of this paragraph are not required if such results or samples have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $1.50 for each capsule in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) and (*c*) of this section; $3.00 for the sample submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), (v), and (vi) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.22 Penicillin-streptomycin-neomycin-polymyxin ointment; penicillin-dihydrostreptomycin-neomycin-polymyxin ointment.

Penicillin-streptomycin-neomycin-polymyxin ointment and penicillin-dihydrostreptomycin-neomycin-polymyxin ointment conform to all requirements and are subject to all procedures prescribed by § 146a.89 for penicillin-streptomycin-neomycin ointment and penicillin-dihydrostreptomycin-neomycin ointment, except that:

(a) They may contain diethylaminoethyl ester penicillin G hydriodide. The diethylaminoethyl ester penicillin G hydriodide used conforms to the requirements prescribed by § 146a.74 (a), except § 146a.74 (a) (2), (3) and (4).

(b) They contain not less than 25,000 units of polymyxin B per single-dose container. The polymyxin B used conforms to the requirements prescribed for polymyxin B by § 146b.107 (a) of this chapter, except the standard for toxicity.

(c) [Reserved.]

(d) In addition to complying with the requirements of § 146a.89 (c), a person who requests certification of a batch shall submit with his request a statement showing the number of units of polymyxin in each gram of the batch, the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the polymyxin B used in making the batch for potency. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the polymyxin used in making the batch.

(e) The fee for the services rendered with respect to the sample submitted in accordance with paragraph (d) of this section shall be $4.00 for each immediate container of the polymyxin used in making the batch.

§ 146a.23 Penicillin-streptomycin-erythromycin ointment; penicillin-dihydrostreptomycin-erythromycin ointment.

Penicillin-streptomycin-erythromycin ointment and penicillin-dihydrostreptomycin-erythromycin ointment conform to all requirements and are subject to all procedures prescribed by § 146a.54 for penicillin-streptomycin ointment and penicillin-dihydrostreptomycin ointment, except that:

(a) They contain not less than 8.0 milligrams of erythromycin per gram. The erythromycin used conforms to the standards prescribed by § 146b.121 (a) of this chapter.

(b) In addition to complying with the requirements of § 146a.54(c), a person who requests certification of a batch shall submit with his request a statement showing the number of milligrams of erythromycin in each gram of the batch, the batch mark, and (unless they were previously submitted), the results and the date of the latest tests and assays of the erythromycin used in making the batch for potency, moisture, pH, and color-identity test. He shall also submit in connection with his request a sample consisting of not less than 7 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the erythromycin used in making the batch.

(c) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (b) of this section shall be:

(1) $6.00 for each immediate container of the ointment;

(2) $4.00 for each immediate container of erythromycin used in making the ointment.

§ 146a.24 Sodium penicillin (penicillin sodium, penicillin sodium salt), calcium penicillin (penicillin calcium, penicillin calcium salt), crystalline penicillin (crystalline penicillin sodium, crystalline penicillin sodium salt, crystalline penicillin potassium, crystalline penicillin potassium salt, crystalline penicillin G sodium, crystalline penicillin G sodium salt, crystalline penicillin G potassium, crystalline penicillin G potassium salt, crystalline penicillin O sodium, crystalline penicillin O sodium salt, crystalline penicillin O potassium, crystalline penicillin O potassium salt).

(a) *Standards of identity, strength, quality, and purity.* Sodium penicillin is the sodium salt of a kind of penicillin, or a mixture of two or more such salts; calcium penicillin is the calcium salt of a kind of penicillin, or a mixture of two or more such salts; crystalline penicillin is the heat-stable crystalline sodium or potassium salt of one or more kinds of penicillin, but the quantity of any salt of penicillin K therein is not more than 30 percent; crystalline penicillin G is crystalline penicillin which contains not less than 85 percent by weight of the sodium salt or potassium salt of penicillin G; crystalline penicillin O is crystalline penicillin which contains not less than 85 percent by weight of the sodium salt or potassium salt of penicillin O and it contains not more than 0.5 percent by weight of the sodium salt or potassium salt of penicillin G. Each such drug is so purified and dried that:

(1) Its potency is not less than 500 units per milligram, except that if it contains not less than 90 percent of a salt of penicillin X its potency is not less than 350 units per milligram;

(2) It is sterile;

(3) It is nontoxic;

(4) It is nonpyrogenic;

(5) Its moisture content is not more than 2.5 percent unless it is crystalline penicillin in which case its moisture content is not more than 1.5 percent;

(6) Its pH in aqueous solution of 30 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness; each such container shall contain 100,000 units, 200,000 units, 300,000 units, 500,000 units, 1,000,000 units, 2,000,000 units, 3,000,000 units, 4,000,000 units, or 5,000,000 units, except that when packaged and labeled solely for dental use each such container may contain not less than 10,000 units and except that when packaged and labeled for intravenous infusion only each such container may contain 20,000,000 units, and each may be packaged in combination with a container of the solvent, water for injection U.S.P., dextrose injection 5 percent U.S.P. (if not packaged for dental use), sodium chloride solution U.S.P. or an aqueous solution of a suitable local anesthetic.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 18 months, or if it is crystalline penicillin, 36 months, after the month during which the batch was certified.

(ii) On the immediate container, the statement "Sterile solution may be kept in refrigerator for __ days without significant loss of potency," the blank being filled in with the figure "3" if it is crystalline penicillin or with the figure "7" if it is not crystalline penicillin, unless such information is contained in the labeling within the package from which it is dispensed.

(iii) On the outside wrapper or container, if it is not crystalline penicillin, the statement "Store in refrigerator not above 15° C. (59° F.)."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except

that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(3) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The number of units of penicillin per milligram or per gram and the number of grams or kilograms in the immediate container.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The information required by subparagraph (1) (i) and (iii) of this paragraph.

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH, penicillin K content (unless it is crystalline penicillin G or crystalline penicillin O), crystallinity and heat stability if it is crystalline penicillin, the penicillin G content if it is crystalline penicillin G or crystalline penicillin O, and the penicillin O content if it is crystalline penicillin O. If such batch or any part thereof is to be packaged with a solvent such request shall also be acompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) If such batch is packaged for dispensing, such person shall submit with his request a sample consisting of 10 immediate containers for sterility testing and, for all tests except sterility, one immediate container for each 5,000 immediate containers in the batch but in no case less than the following quantities (excluding the 10 containers submitted for sterility):

(i) If it is not crystalline penicillin, not less than 6 immediate containers:

(ii) If it is crystalline penicillin, other than crystalline penicillin G or crystalline penicillin O, not less than 8 immediate containers;

(iii) If it is crystalline penicillin G or crystalline penicillin O, not less than 10 immediate containers; or

(iv) If it is packaged in containers of less than 100,000 units each for dental use, not less than 20 immediate containers if it is not crystalline penicillin, and not less than 40 immediate containers if it is crystalline penicillin.

Such sample shall be collected by taking single immediate containers before or after labeling, at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(3) If such batch is packaged for repacking or for use in the manufacture of another drug, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 6 packages, or in the case of crystalline penicillin 10 packages, containing approximately equal portions of not less than 60 milligrams each.

(ii) For sterility testing; 10 packages, each containing approximately 300 milligrams.

Each such portion shall be taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(4) In connection with contemplated requests for certification of repacked batches or batches of another drug in the manufacture of which it is to be used, the manufacturer of a batch which is to be so repacked or used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (3) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i), (ii), and (iii), (3) (i), and (4) of this section; $1.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) (iv) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of crystalline penicillin G from certification.* Crystalline penicillin G sodium, crystalline penicillin G sodium salt, crystalline penicillin G potassium, crystalline penicillin G potassium salt, shall be exempt from the requirements of sections 502 (l) and 507 of the act. No provision of any regulation in this part shall apply to such drug except the standards of identity, strength, quality, and purity specified for its use in the manufacture of another drug.

§ 146a.25 Penicillin in oil and wax (calcium penicillin in oil and wax, crystalline penicillin in oil and wax).

(a) *Standards of identity, strength, quality, and purity.* Penicillin in oil and wax is a suspension of calcium penicillin or crystalline penicillin in a menstruum of refined peanut oil or sesame oil in which white wax is dispersed. If it is represented to be free-flowing, not less than 50 percent of the total relative weight of the penicillin in the drug consists of penicillin having a particle size of not less than 50 microns in length. Its potency is 100,000 units, 200,000 units, or 300,000 units per milliliter except if it is packaged and labeled solely for udder instillations of cattle its potency is 2,000 units per milliliter. The content of white wax in the menstruum before the addition of the penicillin is not less than 3.0 percent (w/v) if the potency is to be not more than 200,000 units per milliliter, and not less than 4.7 or more than 4.9 percent (w/v) if the potency is to be 300,000 units per milliliter. The moisture content is not more than 1.0 percent. It is sterile. The calcium penicillin or crystalline penicillin used conforms to the requirements of § 146a.24 (a), but its potency is not less than 750 units per milligram if it is used in making a product of not more than 200,000 units per milliliter, and not less than 900 units per milligram if it is used in making a product containing 300,000 units per milliliter. The peanut oil, sesame oil, and the white wax used conform to the standards prescribed therefor by the U. S. P.

(b) *Packaging.* The immediate container of penicillin in oil and wax shall be of colorless transparent glass (if packaged and labeled solely for udder instillations of cattle, it shall be of transparent glass) so closed as to be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that its contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are

normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The quantity of penicillin in oil and wax in each such container shall be not less than one milliliter and not more than 20 milliliters, unless it is packaged for repacking or is packaged and labeled solely for udder instillations of cattle. Unless it is packaged for repacking each container shall be filled with a volume of penicillin in oil and wax in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated whether administered in either single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in, if crystalline penicillin is used, with the date that is 18 months, or if crystalline penicillin is not used, with the date that is 12 months after the month during which the batch was certified.

(ii) On the outside wrapper or container and the immediate container, the statements "Do not heat" and "Shake well," if it is represented to be free flowing.

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin in oil and wax shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that the peanut oil or sesame oil and white wax used in making such batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture, and if it is represented to be free-flowing, the particle size of the penicillin.

(ii) The penicillin used in making the batch; potency, sterility, toxicity, pyrogens, moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity and heat stability if it is crystalline penicillin, and the penicillin G content if it is crystalline penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: One package for each 5,000 packages in the batch, but in no case less than 5 packages.

(*b*) For sterility testing; 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch:

(*a*) For all tests except sterility; 6 packages if it is calcium penicillin or 10 packages if it is crystalline penicillin, each containing approximately equal portions of not less than 60 milligrams.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of not less than 300 milligrams.

Such samples shall be packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, the peanut oil or sesame oil and white wax used in making the batch; one package of each containing, respectively, approximately 250 grams and 25 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin in oil and wax under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), and (ii) (*a*), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.26 Penicillin ointment.

(a) *Standards of identity, strength, quality, and purity.* Penicillin ointment is calcium penicillin, crystalline penicillin, procaine penicillin, or *l*-ephenamine penicillin G in a suitable and harmless ointment base, with or without a suitable anesthetic. If it is intended solely for veterinary use and is conspicuously so labeled, it may contain nitrofurazone and a suitable and harmless salt of cobalt. Its moisture content is not more than 1.0 percent. Its potency is not less than 250 units per gram, except if it is packaged and labeled solely for udder instillations of cattle, its potency is not less than 2,000 units per gram. The calcium penicillin or crystalline penicillin used conforms to the requirements of § 146a.24(a), except the limitation on penicillin K content, and except § 146a.24(a) (1), (2), (3), and (4), but its potency is not less than 300 units per milligram. The procaine penicillin used conforms to the requirements of § 146a.44(a), except § 146a.44(a) (2), (3), and (4). The *l*-ephenamine penicillin G used conforms to the requirements of § 146a.64(a), except § 146a.64 (a) (2), (3), and (4). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless it is intended solely for veterinary use, penicillin ointment shall be packaged in collapsible tubes, which shall be well-closed containers as defined by the U. S. P., and shall not be larger than the ⅛-ounce size if such ointment is represented for ophthalmic use, and in no case larger than the 2-ounce size. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of

this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is not more than 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) On the outside wrapper or container, the statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)," unless the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section after having been stored at room temperature; but in no case shall such statement be required if it is labeled with an expiration date that is 9 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin ointment shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that each component of the ointment base used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The penicillin used in making the batch; potency, moisture, pH, crystallinity if it is a crystalline salt of penicillin, heat stability if it is crystalline penicillin or *l*-ephenamine penicillin G, the penicillin G content if it is penicillin G, and the specific rotation if it is *l*-ephenamine penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one package for each 5,000 packages in the batch, but in no case less than 5 packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 5 packages, or in the case of crystalline penicillin, 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is not procaine penicillin, and not less than 300 milligrams if it is procaine penicillin, packaged in accordance with the requirements of § 146a.24 (b) or § 146a.44 (b).

(iii) In case of an initial request for certification, the ingredients used in making the batch; one package of each containing approximately 200 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin ointment under the regulations in this part shall be:

(1) $4.00 for each package in the sample submitted in accordance with paragraph (d) (3) (i) of this section, $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii), of this section; and

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.27 Penicillin tablets.

(a) *Standards of identity, strength, quality, and purity.* Penicillin tablets are tablets composed of sodium penicillin, calcium penicillin, potassium penicillin, crystalline penicillin O, crystalline penicillin V, crystalline potassium penicillin V, benzathine penicillin G or procaine penicillin, with or without one or more suitable sympathomimetic agents, analgesic substances, antihistaminics, and caffeine and with or without one or more suitable and harmless vitamin substances, buffer substances, diluents, binders, lubricants, colorings, and flavorings. They may also contain probenecid or one or more suitable sulfonamides. The potency of each tablet is not less than 50,000 units, and if it is less than 100,000 units it is unscored. Its moisture content is not more than 1.0 percent if it contains sodium penicillin, calcium penicillin, potassium penicillin, or crystalline penicillin O; not more than 2.0 percent if it contains procaine penicillin; not more than 3.0 percent if it contains crystalline penicillin V; and not more than 8.0 percent if it contains benzathine penicillin G. If it contains crystalline potassium penicillin V, its moisture content is not more than 1.5 percent unless the person who requests certification has submitted to the Commissioner information adequate to prove that his drug is stable when it has a moisture content not exceeding 3 percent. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. The penicillin used conforms to the standards prescribed for such drug by the regulations in this chapter, except the standards for sterility and pyrogens. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each penicillin tablet is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. If the penicillin tablets are freely soluble, each immediate container may be packaged in combination with one immediate container of a suitable and harmless aqueous vehicle with or without one or more suitable sulfonamides.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) If the batch contains buffer substances, the name of each substance.

(ii) The statement "Expiration date _____," the blank being filled in with one of the following dates after the month during which the batch was certified:

(*a*) If a crystalline penicillin is not used, 12 months.

(*b*) If a crystalline penicillin is used and it contains a vitamin substance, 18 months.

(*c*) If a penicillin V or potassium penicillin V is used and it does not contain a vitamin substance, 24 months.

(*d*) If a crystalline penicillin other than a penicillin V is used and it does not contain a vitamin substance, 36 months.

(*e*) In lieu of the expiration date prescribed in (*a*), (*b*), (*c*), and (*d*) of this subdivision, if the person who requests certification has submitted to the Commissioner results of tests and assays that show such drug as prepared by him is stable for 24 months, 36 months, 48 months, or 60 months, such date may be used for such drug.

(iii) If it contains, in addition to penicillin, one or more of the other active ingredients specified in paragraph (a) of this section, after the name "penicillin tablets," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of each other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of tablets in such batch, the number of tablets of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each tablet, the date on which the latest assay of the drug comprising such batch was completed, the date (unless submitted previously) on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed, average moisture of tablets collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH, penicillin K content (unless it is crystalline penicillin G, crystalline penicillin O, crystalline penicillin V, or crystalline potassium penicillin V), crystallinity if it is crystalline penicillin; heat stability if it is crystalline sodium penicillin, potassium penicillin, or crystalline penicillin O; the penicillin G content if it is a penicillin G or crystalline penicillin O; the penicillin V content if it is a penicillin V; and the penicillin O content if it is crystalline penicillin O.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For potency and moisture:

(*1*) If the person who requests certification is the manufacturer of the batch: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets collected by taking single tablets at such intervals throughout the entire time of tableting the batch that the quantities tableted during the intervals are approximately equal;

(2) If, after tableting, such person packaged the batch into dispensing-size containers: 20 tablets collected at equal intervals during each day the tablets are being packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed; or

(3) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of tablets filled by such person into dispensing-size containers during each day's packaging operations): One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets that the quantities packaged during the intervals are approximately equal.

(*b*) For disintegration time: 6 tablets.

(ii) The penicillin used in making the batch; 6 packages, or in the case of crystalline penicillin 10 packages, each containing approximately equal portions of not less than 60 milligrams, except that if it is procaine penicillin, benzathine penicillin G, penicillin V, or potassium penicillin V each package shall contain not less than 300 milligrams, packaged in accordance with the requirements of § 146a.24 (b), 146a.44 (b), 146a.68 (b), or 146a.103 (b).

(iii) In case of an initial request, each other substance used in making the batch; one package of each, containing approximately 5 grams, and if the batch or any part thereof is to be packaged in combination with an aqueous vehicle, or when any change is made in the composition of such vehicle, five packages of the vehicle included in the combination.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin tablets under the regulations in this part shall be:

(1) $0.75 for each tablet in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) (*1*) and (3) of this section; $3.00 for the samples submitted in accordance with paragraph (d) (3) (i) (*a*) (2) and (*b*) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such tablets and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of penicillin tablets from certification.* Penicillin tablets, with or without added vitamin substances and residues from streptomyces fermentation, shall be exempt from the requirements of sections 502(*l*) and 507 of the act, if they comply with the following conditions:

(1) They contain not more than 1,000 units per tablet.

(2) The outside wrapper or container and the immediate container bear an expiration date that is not more than 36 months after the month during which the batch was last assayed and released by the manufacturer.

(3) They are intended to be administered only in the drinking water of poultry for use solely as a feed supplement and are conspicuously so labeled; they are not represented for the prevention or treatment of disease; and their labeling bears adequate directions for use by laymen.

§ 146a.28 Crystalline penicillin G oral suspension, crystalline penicillin G sodium oral suspension, potassium penicillin G oral suspension.

(a) *Standards of identity, strength, quality, and purity.* Crystalline penicillin G oral suspension is crystalline penicillin G sodium or potassium penicillin G and one or more suitable and harmless suspending or dispersing agents and preservatives, with or without probenecid or one or more suitable sulfonamides and suitable and harmless buffer substances, colorings, and flavorings, suspended in a suitable and harmless vehicle. Its potency is not less than 20,000 units per milliliter. Its moisture content is not more than 1.0 percent. The crystalline penicillin used conforms to § 146a.24(a), except § 146a.24(a) (2) and (4). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container shall be a tight container as de-

fined by the U. S. P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its outside wrapper or container and the immediate container the following:

(i) If the batch contains buffer substances, the name of each such substance.

(ii) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that if the person who requests certification has submitted to the Commissioner results of tests and assays that show such drug as prepared by him is stable for 36 months, such date may be used for such drug.

(iii) If it contains, in addition to penicillin, one or more of the other active ingredients specified in paragraph (a) of this section, after the name "crystalline penicillin G oral suspension," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of each such other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin G used in making such batch was completed, the potency per milliliter of the batch, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per milliliter and moisture.

(ii) The penicillin G used in making the batch; potency, toxicity, pH, moisture, crystallinity, and the penicillin G content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin G used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; 1 package of each containing approximately 5.0 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than the examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.29 Penicillin with aluminum hydroxide gel.

(a) *Standards of identity, strength, quality, and purity.* Penicillin with aluminum hydroxide gel is a packaged combination of one immediate container of penicillin and one immediate container of aluminum hydroxide gel. Such penicillin conforms to the standards prescribed therefor by § 146a.24(a), except subparagraphs (1) and (4) of § 146a.24 (a), but its potency is not less than 300 units per milligram. Such aluminum hydroxide gel conforms to the standards prescribed therefor by the U.S.P., but contains not more than 50 viable microorganisms per milliliter.

(b) *Packaging.* The immediate container of the penicillin shall conform to the packaging requirements set forth in § 146a. 24 (b), except that it shall contain not less than 300,000 units and its closure may be one through which a hypodermic needle cannot be introduced. The immediate container of the aluminum hydroxide gel shall be a tight container as defined by the U. S. P.; the quantity therein shall be 30 milliliters for each 100,000 units in the immediate container of penicillin.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container of penicillin, the statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified, unless it is crystalline penicillin, in which case the blank is filled in with the date that is 36 months after the month during which the batch was certified.

(ii) On the immediate container of the penicillin, the statement "Warning—Not for injection," unless it conforms to the standards and packaging requirements prescribed therefor by § 146a.24 (a) and (b), except that the immediate container may contain 300,000 units.

(iii) On the immediate container of the aluminum hydroxide gel, the conditions under which the mixture should be stored, including a reference to its instability when stored under other conditions, and the statement "The mixture may be kept in refrigerator for 1 week without significant loss of potency," unless such information is contained in the circular or other labeling within or attached to the package.

(iv) On the outside wrapper or container and the immediate container of the aluminum hydroxide gel:

(*a*) A statement giving the method for dissolving the penicillin in the aluminum hydroxide gel.

(*b*) The potency per milliliter after the penicillin has been dissolved therein.

(v) On the outside wrapper or container if it is not crystalline penicillin, the statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin for inclusion in such combination shall submit with his request a statement showing the batch mark of the penicillin, the number of packages thereof in such batch, the number of units in the immediate container thereof, and (unless it was previously

submitted) the date on which the latest assay of the penicillin included in such combination was completed, and a statement that the aluminum hydroxide gel conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph such person shall submit in connection with his request results of the tests and assays made by him on an accurately representative sample of the penicillin for potency, sterility, toxicity, moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity and heat stability if it is crystalline penicillin, and the penicillin G content if it is crystalline penicillin G.

(3) If the penicillin has not been certified previously, such person shall submit in connection with his request a sample of the batch consisting of one package for each 5,000 packages in the batch, but in no case less than 6 packages except that in the case of crystalline penicillin other than crystalline penicillin G such sample shall consist of not less than 8 packages, and in the case of crystalline penicillin G not less than 10 packages. Such sample shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(4) No result referred to in subparagraph (2) of this paragraph is required if such result has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch of penicillin for inclusion in combination with aluminum hydroxide gel under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) of this section, or $2.00 if no such sample is submitted. and

(2) If the Commissioner considers that investigations, other than examination of such containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subpargraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.30 Penicillin troches.

(a) *Standards of identity, strength, quality, and purity.* Penicillin troches are troches composed of sodium penicillin, calcium penicillin, potassium penicillin, procaine penicillin, *l*-ephenamine penicillin G, or crystalline penicillin O and one or more suitable or harmless diluents, binders, and lubricants, with or without one or more suitable and harmless local anesthetics, chemical antimicrobial agents, masticatory substances, colorings, and flavorings. The potency of each troche is not less than 500 units; the moisture content is not more than 1.0 percent, except that if flavorings are omitted and it contains crystalline penicillin in a base of not less than 50 percent gelatin by weight, its moisture content is not more than 2 percent. The sodium penicillin, calcium penicillin, crystalline penicillin O, or potassium penicillin used conforms to the requirements of § 146a.24 (a) except the limitation on penicillin K content and except subparagraphs (1), (2), and (4) of § 146a.24 (a), but the potency is not less than 300 units per milligram. The procaine penicillin used conforms to the requirements of § 146a.44 (a), except the limitation on penicillin K content and except subparagraphs (2) and (3) of § 146a.44 (a). The *l*-ephenamine penicillin G used conforms to the requirements of § 146a.64 (a), except subparagraphs (2) and (3) of that paragraph. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each penicillin troche is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the troches by a plug of cotton or other like material. The composition of the immediate container, or foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106 (b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container, the statement "Expiration date_____," the blank being filled in, if crystalline penicillin, procaine penicillin, *l*-ephenamine penicillin G, or crystalline penicillin O is not used, with the date that is 9 months; or if crystalline penicillin, procaine penicillin, *l*-ephenamine penicillin G, or crystalline penicillin O is used, with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) On the outside wrapper or container, if crystalline penicillin, procaine penicillin, *l*-ephenamine penicillin G, or crystalline penicillin O is not used, the statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)."

(3) On the label and labeling, wherever the name "penicillin troches" appears:

(i) Immediately preceding such name, if a masticatory substance is present, the word "chewing" or "masticatory."

(ii) Immediately following such name, if a local anesthetic and/or a chemical antimicrobial agent is present the words "with _____," the blank being filled in with the common or usual name of each such other ingredient present.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of troches in such batch, the number of troches of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each troche, the date on which the latest assay of the drug comprising such batch was completed, the batch mark and date (unless submitted previously) on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency and average moisture of troches collected during time of making them, and, unless the troches are packaged into dispensing-size containers immediately after they are manufactured, average moisture of troches collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency and average moisture of troches collected during each day the troches are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH; crystallinity if it is crystalline penicillin; specific rotation if it is *l*-ephenamine penicillin G; heat stability if it is crystalline sodium penicillin, potassium penicillin, *l*-ephenamine penicillin G, or crystalline penicillin O; the penicillin G content if it is crystalline sodium penicillin G, potassium penicillin G, or crystalline penicillin O; the procaine penicillin G content if it is crystalline procaine penicillin G; the *l*-ephenamine penicillin G content if it is *l*-ephenamine penicillin G, and the penicillin O content if it is crystalline penicillin O.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such

person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: One troche for each 5,000 troches in the batch, but in no case less than 30 troches collected by taking single troches at intervals throughout the entire time of making them that the quantities made during the intervals are approximately equal;

(*b*) If, after manufacturing, such person packages the batch into dispensing-size containers: 20 troches collected at equal intervals during each day the troches are being packaged, except that this sample is not required if the troches are packaged immediately after they are manufactured;

or

(*c*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of troches filled by such person into dispensing-size containers during each day's packaging operations); one troche for each 5,000 troches, but in no case less than 30 troches collected by taking single troches at such intervals throughout each day of packaging the troches that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 5 packages, or in the case of crystalline penicillin 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is not procaine penicillin or *l*-ephenamine penicillin G, and not less than 300 milligrams if it is procaine penicillin or *l*-ephenamine penicillin G, packaged in accordance with the requirements of § 146a.24 (b), § 146a.44 (b), or § 146a.64 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the service rendered with respect to each batch of penicillin troches under the regulations in this part shall be:

(1) $0.75 for each troche without masticatory substance in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) and (*c*) of this section; $2.00 for each troche with masticatory substance in such sample; $3.00 for the sample submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such troches, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations. The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of penicillin troches from certification.* Penicillin troches shall be exempt from the requirements of sections 502(l) and 507 of the act if the drug complies with all the following conditions:

(1) It conforms to the standards of identity, strength, quality, and purity prescribed by paragraph (a) of this section.

(2) It does not contain crystalline penicillin O or *l*-ephenamine penicillin G.

(3) It conforms to the packaging requirements prescribed by paragraph (b) of this section.

(4) Its labeling conforms to the requirements prescribed by paragraph (c) of this section and its labeling as required by § 1.106(b) (3) of this chapter bears information that the drug is for use only as a local treatment for Vincent's infection (Vincent's angina) and as an adjunct in pericoronitis and other superficial infections due to penicillin-sensitive organisms.

(5) The label bears an expiration date 9 months after the month in which the batch was last assayed and released by the manufacturer if it does not contain a crystalline penicillin, or 12 months if it does contain a crystalline penicillin, except that the date that is 18 months, or 24 months, or 36 months, or 60 months may be used if the manufacturer has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by paragraph (a) of this section.

§ 146a.31 Penicillin dental cones (calcium penicillin dental cones, penicillin dental cones calcium salt, crystalline penicillin dental cones).

(a) *Standards of identity, strength, quality, and purity.* Penicillin dental cones are composed of calcium penicillin or crystalline penicillin and one or more suitable and harmless diluents, binders, and lubricants, with or without a suitable local anesthetic and with or without one or more suitable sulfonamides. The potency of each cone is not less than 500 units. Its moisture content is not more than 1.0 percent. If a sulfonamide is used its quantity is not less than 0.032 gram per cone. The penicillin used conforms to the requirements of § 146a.24 (a) except the limitation on penicillin K content and except subparagraphs (1), (2), and (4) of § 146a.24(a), but its potency is not less than 300 units per milligram. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each penicillin dental cone is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the cones by a plug of cotton or other like material. The composition of the immediate container, or foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the regulations prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label and labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in, if crystalline penicillin is used, with the date that is 36 months, or if crystalline penicillin is not used, with the date that is 12 months after the month during which the batch was certified.

(ii) If it contains, in addition to penicillin, one or more of the other active ingredients specified in paragraph (a) of this section, after the name "penicillin dental cones," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of each such other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of dental cones in such batch, the number of dental cones of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each dental cone, the date on which the latest assay of the drug comprising such batch was completed, the date (unless submitted previously) on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch:

Average potency and average moisture of cones collected during the time of making the batch, and, unless the cones are packaged into dispensing-size containers immediately after they are compressed, average moisture of cones collected during each day of packaging the batch.

(b) If the person who requests certification is not the manufacturer of the batch: Average potency and average moisture of cones collected during each day the cones are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH, crystallinity, and heat stability if it is crystalline penicillin and the penicillin G content if it is crystalline penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(a) If the person who requests certification is the manufacturer of the batch: One cone for each 5,000 cones in the batch, but in no case less than 30 cones collected by taking single cones throughout the entire time of making the batch that the quantities made during the intervals are approximately equal.

(b) If, after making, such person packages the batch into dispensing-size containers: 20 cones collected at equal intervals during each day the cones are being packaged, except that this sample is not required if the cones are packaged immediately after they are made; or

(c) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of cones filled by such person into dispensing-size containers during each day's packaging operations): One cone for each 5,000 cones in the batch, but in no case less than 30 cones collected by taking single cones at such intervals throughout each day of packaging the cones that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; five packages if it is calcium penicillin or 10 packages if it is crystalline penicillin containing approximately equal portions of not less than 60 milligrams each, packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin dental cones under the regulations in this part shall be:

(1) $0.75 for each cone in the samples submitted in accordance with paragraph (d) (3) (i) (a) and (c) of this section; $3.00 for the sample submitted in accordance with paragraph (d) (3) (i) (b) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such cones and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.32 Penicillin with vasoconstrictor; penicillin with _____ (the blank being filled in with the common or usual name of the vasoconstrictor).

(a) *Standards of identity, strength, quality, and purity.* Penicillin with vasoconstrictor is a dry mixture of penicillin and a suitable vasoconstrictor with or without suitable buffer substances and preservatives, or it is a packaged combination of one immediate container of penicillin and one immediate container of an aqueous solution of a suitable vasoconstrictor. The penicillin is of such quantity that when dissolved as directed the potency of such solution is not less than 500 units per milliliter after it has been kept for 7 days at a temperature of 15° C. (59° F.). Such solution is isotonic and has a pH of 6, ±0.2. The moisture content of the dry mixture of penicillin with vasoconstrictor is not more than 1.5 percent. The penicillin used conforms to the requirements of § 146a.24 (a), except the limitation on penicillin K content and except subparagraphs (2) and (4) of that paragraph. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Each immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The immediate container of the dry mixture of penicillin with vasoconstrictor may be packaged in combination with an immediate container of a suitable aqueous diluent.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container of penicillin, if it is a packaged combination of one immediate container of penicillin and one immediate container of a vasoconstrictor, the statement "Expiration date _____," the blank being filled in with the date that is 18 months, or if it is crystalline penicillin 36 months, after the month during which the batch was certified; if it is the dry mixture of penicillin with vasoconstrictor, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) On the outside wrapper or container and on the immediate container of the solution in the packaged combination:

(a) A statement giving the method of dissolving the penicillin, and if it is not a packaged combination, a statement that distilled water U.S.P. should be used.

(b) The potency per milliliter after the penicillin has been dissolved therein.

(c) If it is a packaged combination of one immediate container of penicillin and one immediate container of vasoconstrictor and it is not crystalline penicillin, the statement "Store in refrigerator not above 15° C. (59° F.)."

(d) The conditions under which the solution should be stored, including a reference to its instability when stored under other conditions, and a statement "The solution may be kept in a refrigerator for 1 week without significant loss of potency."

(e) The statement "*Warning*—Not for injection."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warning adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter a person who requests certification of a batch of penicillin with vasoconstrictor shall submit with his request a statement showing the batch mark, the number of packages thereof in such batch, the number of units in each immediate container thereof, and (unless it was previously submitted) the date on which the latest assay of the penicillin included in such batch was completed, the quantity of each ingredient used in making the batch of the dry mixture of penicillin with vasoconstrictor, the quantity of each ingredient used in making the solution included in the packaged combination, and a statement that such solution conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The penicillin included in the packaged combination and the penicillin used in making the batch of the dry mixture of penicillin with vasoconstrictor; potency, toxicity, moisture, pH, crystallinity and heat stability, if it is

crystalline penicillin, and the penicillin G content if it is crystalline penicillin G.

(ii) The solution after the penicillin has been dissolved therein; potency.

(iii) The batch of the dry mixture of penicillin with vasoconstrictor; potency, moisture content.

(3) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If it contains only penicillin and the penicillin used has been previously submitted, or it contains penicillin and other ingredients; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, unless it is in tablet form in which case such sample shall consist of not less than 30 nor more than 100 tablets.

(*b*) If it contains only penicillin and the penicillin used has not been previously submitted; one immediate container or tablet for each 5,000 immediate containers or tablets, but in no case less than 40 immediate containers or tablets.

Such sample shall be collected by taking single immediate containers or tablets at such intervals throughout the entire time of packaging or tableting the batch that the quantities packaged or tableted during the intervals are approximately equal.

(ii) The penicillin used in making the batch of the dry mixture of penicillin with vasoconstrictor; 5 packages, or in the case of crystalline penicillin 10 packages, each containing approximately equal portions of not less than 60 milligrams each, packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification of a batch of a dry mixture of penicillin with vasoconstrictor, each other substance used in making the batch; one package of each containing approximately 5 grams.

(iv) In case of an initial request for certification of the packaged combination of penicillin with vasoconstrictor, or when any change is made in the composition of such solution; five packages of the solution included in the combination.

(4) No result referred to in subparagraph (2) (i) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, are required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin with vasoconstrictor under the regulations in this part shall be:

(1) $0.75 for each tablet submitted in accordance with paragraph (d) (3) (i) (*a*) and (*b*) of this section; $1.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; and $4.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), (iii), and (iv) of this section

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.33 Penicillin for surface application.

(a) *Standards of identity, strength, quality, and purity.* Penicillin for surface application is calcium penicillin and one or more of the diluents sodium chloride, milk sugar, sodium citrate, and dextrose. Its moisture content is not more than 1.0 percent. The penicillin used conforms to the requirements of § 146a.24(a), except the limitation of penicillin K content and except subparagraphs (1), (2), and (4) of § 146a.24 (a), but its potency is not less than 300 units per milligram. Each diluent conforms to the standards prescribed therefor by the U. S. P.

(b) *Packaging.* Unless the penicillin for surface application is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each immediate container (except when its content is two or more foil or film enclosures) and each foil or film enclosure shall contain not less than 10,000 units or more than 50,000 units and shall be so sealed that the contents cannot be used without destroying such seal.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(*b*) In case the drug is not sterile, the statement "Not sterile—Not for injection—Not to be used in deep wounds or body cavities."

(ii) On the immediate container, the conditions under which solutions of penicillin for surface application should be stored, including a reference to their instability when stored under other conditions, and the statement "The mixture may be kept in refrigerator for 1 week without significant loss of potency," unless such information is contained in the circular or other labeling within or attached to the package.

(iii) On the outside wrapper or container the statement "Store in refrigerator not above 15° C. (59° F.)."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin for surface application shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each immediate container or foil or film enclosure, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that the sodium chloride, milk sugar, sodium citrate, and dextrose used in making such batch conform to the standards prescribed therefor by the U. S. P.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per immediate container or foil or film enclosure, moisture.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container or, if the drug is packed in foil or film enclosures, one such enclosure for each 5,000 such containers or enclosures in the batch, but in no case less than 20 such containers or enclosures, collected by taking single containers or enclosures at such intervals throughout the entire time of packaging the batch, that the quantities packed during the intervals are approximately equal.

(ii) The penicillin used in making the batch; five packages containing approximately equal portions of not less than 60 milligrams each, packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin for surface application under the regulations in this part shall be:

(1) $1.00 for each immediate container or foil or film enclosure, whichever is the greatest number, in the samples submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such containers or enclosures, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.34 Tablets aluminum penicillin.

(a) *Standards of identity, strength, quality, and purity.* Tablets aluminum penicillin are tablets composed of aluminum penicillin and sodium benzoate, with or without one or more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. The potency of each tablet is not less than 50,000 units, and if it is less than 100,000 units it is "unscored". Each tablet contains 0.3 gram of sodium benzoate. Its moisture content is not more than 2 percent. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. The aluminum penicillin used conforms to the requirements of § 146a.42(a) for aluminum penicillin except subparagraphs (2) and (3) thereof. Each other substance used in the preparation of aluminum penicillin tablets, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each tablet aluminum penicillin is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The number of tablets in the immediate container is such that the total number of units therein is not less than 300,000.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) On the outside wrapper or container, the statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of tablets in such batch, the number of tablets of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each tablet, the date on which the latest assay of the drug comprising such batch was completed, the batch mark and date (unless submitted previously) on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed, average moisture of tablets collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency, average moisture, and, if required by paragraph (a) of this section, disintegration time of tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) The aluminum penicillin used in making the batch; potency, moisture, pH, toxicity, and penicillin K content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For potency and moisture:

(*1*) If the person who requests certification is the manufacturer of the batch: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets collected by taking single tablets at such intervals throughout the entire time of tableting the batch that the quantities tableted during the intervals are approximately equal;

(*2*) If, after tableting, such person packages the batch into dispensing-size containers: 20 tablets collected at equal intervals during each day the tablets are being packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed; or

(*3*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification a batch shall be that number of tablets filled by such person into dispensing-size containers during each day's packaging operations): One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets that the quantities packaged during the intervals are approximately equal.

(*b*) For distintegration time: 6 tablets.

(ii) The aluminum penicillin used in making the batch; 6 packages, each containing approximately equal portions of not less than 300 milligrams each, packaged in accordance with the requirements of § 146a.42 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately five grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of tablets aluminum penicillin under this part shall be:

(1) $0.75 for each tablet in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) (*1*) and (*3*) of this section; $3.00 for the samples submitted in accordance with paragraph (d) (3) (i) (*a*) (*2*) and (*b*) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such tablets and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the costs of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit

maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.35 Penicillin sulfonamide powder (calcium penicillin sulfonamide powder, crystalline penicillin sulfonamide powder).

(a) *Standards of identity, strength, quality, and purity.* Penicillin sulfonamide powder is composed of calcium penicillin or crystalline penicillin and one or both of the sulfonamides, sulfanilamide and sulfathiazole. It is sterile. Its moisture content is not more than 1.0 percent. The quantity of each sulfonamide used is not more than 0.05 gram for each 100 units of penicillin used. The penicillin used conforms to the requirements of § 146a.24(a) except the limitation on penicillin K content and except subparagraphs (1) and (4) of § 146a.24 (a), but its potency is not less than 300 units per milligram. Each sulfonamide used conforms to the standards prescribed therefor by the U. S. P.

(b) *Packaging.* In all cases, the immediate container of penicillin sulfonamide powder shall be a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, shall be sterile at the time of filling and closing, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. If the penicillin sulfonamide powder is packaged for "dusting" purposes each package shall contain not less than 5,000 units of penicillin. If the penicillin sulfonamide powder is packaged for dental use it shall be packaged in immediate containers of colorless, transparent glass meeting the test for glass containers of type I or type II prescribed by the U. S. P. The glass containers shall be open at both ends, one of which is constricted, both ends shall be capable of closure with rubber stoppers, and each such container shall contain not less than 500 units of penicillin. Each package of penicillin sulfonamide powder for dental use shall contain a suitable device for insufflation purposes.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and immediate container:

(*a*) The statement "Expiration date _____," the blank being filled in, if crystalline penicillin is used, with the date that is 24 months, or if crystalline penicillin is not used, with the date that is 9 months after the month during which the batch was certified.

(*b*) If crystalline penicillin is not used, the statement "Store in refrigerator not above 15° C. (59° F.)."

(ii) On the label and the labeling, after the name "penicillin sulfonamide powder," wherever it appears, the words "with _____," in juxtaposition with such name, the blank being filled in with the name of the sulfonamide used.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin sulfonamide powder shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each container of penicillin sulfonamide powder, the quantity of each ingredient used in making the batch, the date on which the latest assay of the penicillin sulfonamide powder comprising such batch was completed, and that such sulfonamide used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per container, average moisture, sterility.

(ii) The penicillin used in making the batch; potency, sterility, toxicity, moisture, pH, crystallinity and heat stability if it is crystalline penicillin and the penicillin G content if it is crystalline penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, unless each such container is packaged to contain more than 1 gram, in which case the sample shall consist of 1 gram for each 5,000 immediate containers in the batch, but in no case less than 5 grams.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers or 1-gram portions at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch:

(*a*) For all tests except sterility; 5 packages, or in the case of crystalline penicillin 10 packages, each containing approximately equal portions of not less than 60 milligrams.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of not less than 300 milligrams. Such samples shall be packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, each sulfonamide used in making the batch; one package of each containing approximately five grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin sulfonamide powder under the regulation in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii) (*a*), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such penicillin sulfonamide powder and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.36 Penicillin vaginal suppositories.

(a) *Standards of identity, strength, quality, and purity.* Penicillin vaginal suppositories are suppositories composed of sodium penicillin, calcium penicillin, potassium penicillin, or procaine penicillin in a base of spermaceti and cocoa butter. The potency of each suppository is not less than 100,000 units; its moisture content is not more than 1.0 percent. The sodium penicillin, calcium penicillin, and potassium penicillin used conform to the requirements of § 146a.24 (a), except § 146a.24(a) (1), (2), (3), and (4), but its potency is not less than 300 units per milligram. The procaine penicillin used conforms to the requirements of § 146a.44(a), except § 146a.44 (a) (2), (3), and (4). The spermaceti and cocoa butter used conform to the standards prescribed therefor by the U.S.P.

(b) *Packaging.* In all cases, the immediate container of penicillin vaginal suppositories shall be a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor

changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended solely for human use.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) On the outside wrapper or container, the statement "Store in refrigerator not above 15° C. (59° F.)."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of suppositories in such batch, the number of suppositories of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each suppository, the date or which the latest assay of the drug comprising such batch was completed, the date (unless submitted previously) on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency and average moisture of suppositories collected during the time of making the batch, and, unless the suppositories are packaged into dispensing-size containers immediately after they are molded, average moisture of suppositories collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency and average moisture of suppositories collected during each day the suppositories are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch; potency, moisture, pH, penicillin K content (unless it is crystalline sodium, potassium, or procaine penicillin G), crystallinity if it is crystalline penicillin, heat stability if it is crystalline sodium or potassium penicillin, the penicillin G content if it is crystalline sodium or potassium penicillin G, and the procaine penicillin G content if it is procaine penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph such person shall submit in connection with his request in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: One suppository for each 5,000 suppositories in the batch, but in no case less than 30 suppositories collected by taking single suppositories throughout the entire time of making the batch that the quantities made during the intervals are approximately equal.

(*b*) If, after making, such person packages the batch into dispensing-size containers: 20 suppositories collected at equal intervals during each day the suppositories are being packaged, except that this sample is not required if the suppositories are packaged immediately after they are made; or

(*c*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of suppositories filled by such person into dispensing-size containers during each day's packaging operations): One suppository for each 5,000 suppositories in the batch, but in no case less than 30 suppositories collected by taking single suppositories at such intervals throughout each day of packaging the suppositories that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 6 packages, or in the case of crystalline penicillin 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is not procaine penicillin, and not less than 300 milligrams, if it is procaine penicillin, packaged in accordance with the requirements of § 146a.24 (b) or § 146a.44 (b).

(iii) In case of an initial request for certification, the spermaceti and cocoa butter used in making the batch; one package of each containing, respectively, approximately 10 grams and 100 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin vaginal suppositories under the regulations in this part shall be:

(1) $0.75 for each suppository in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) and (*c*) of this section; $3.00 for each sample submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such suppositories and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.37 Buffered crystalline penicillin.

Buffered crystalline penicillin conforms to all requirements prescribed by § 146a.24 for crystalline penicillin, and is subject to all procedures prescribed by § 146a.24 for crystalline penicillin, except that:

(a) It contains the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids; such sodium citrate conforms to the standards prescribed therefor by the U. S. P.;

(b) If it is crystalline penicillin G, the penicillin G content is corrected for the sodium citrate content;

(c) The immediate container, if it is packaged for dispensing, shall bear, in lieu of the statement prescribed for crystalline penicillin by § 146a.24(c) (1) (ii), the statement "Sterile solution may be kept in refrigerator for 1 week without significant loss of potency," unless such information is contained in the circular or other labeling within or attached to the package from which it is dispensed;

(d) A person who requests certification of a batch shall submit with his request a statement showing the quantity of sodium citrate used in making the batch, that such sodium citrate conforms to the requirements prescribed therefor by this section, and in case of an initial request for certification he shall submit an accurately representative sample of such sodium citrate consisting of approximately 5 grams; and

(e) The fee for the services rendered with respect to the sample of sodium citrate submitted in accordance with the requirements prescribed therefor by this section shall be $4.00.

(f) Exemption of buffered crystalline penicillin G from certification: Buffered crystalline penicillin G that conforms to the requirements of this section shall be exempt from the requirements of sections 502 (l) and 507 of the act, if it complies with the following conditions:

(1) The outside wrapper or container and the immediate container bear an expiration date not more than 36 months after the month during which

the batch was last assayed and released by the manufacturer; and

(2) If it is intended for use by man, its labeling as required by § 1.106(b)(3) of this chapter bears information for its use only in the following conditions:

(i) Staphylococcic infections with and without bacteremia.

(ii) Hemolytic streptococcic infections including bacteremia.

(iii) Anaerobic streptococcic infections.

(iv) Pneumococcic infections.

(v) Gonococcic infections.

(vi) Syphilis.

(vii) Anthrax.

(viii) As an adjunct to specific antitoxin therapy for clostridial infections.

(ix) Bacterial endocarditis due to penicillin-sensitive organisms.

(x) Diphtheria, with antitoxin therapy.

(xi) Pulmonary suppuration due to penicillin-sensitive organisms.

(xii) Vincent's infection.

(xiii) Erysipeloid (swine erysipelas).

(xiv) Meningococcic infections.

(xv) For the prevention of possible secondary infection following tonsillectomy and tooth extraction in patients with a history of rheumatic fever or rheumatic heart disease, in congenital heart disease, and in other conditions in which secondary infection may occur; or

(3) It is intended solely for veterinary use and is conspicuously so labeled, and its labeling bears information that the drug is for use only in the treatment of one or more of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Bovine mastitis caused by Streptococcus agalactiae.

(ii) Leptospirosis in dogs.

(iii) Osteomyelitis.

(iv) Peritonitis.

(v) Strangles of horses.

(vi) Equine pneumonia.

(vii) Early tetanus, with antitoxin therapy.

(viii) Calf pneumonia.

(ix) Calf diphtheria.

(x) Pyelonephritis in cattle.

(xi) Blackleg.

(xii) Malignant edema.

(xiii) Early anthrax.

(xiv) Metritis.

(xv) Bovine actinomycosis.

(xvi) Swine erysipelas in turkeys.

If such drug is represented for use in milk-producing animals, its labeling shall bear the statement required by § 146.14 of this chapter.

§ 146a.38 Capsules buffered penicillin with pectin hydrolysate (capsules buffered potassium penicillin with pectin hydrolysate).

(a) *Standards, of identity, strength, quality and purity.* Capsules buffered penicillin with pectin hydrolysate are capsules composed of potassium penicillin with pectin hydrolysate and sodium citrate enclosed in a hard gelatin capsule. The potassium penicillin with pectin hydrolysate is prepared by lyophilizing a solution containing one part potassium penicillin and three parts of pectin hydrolysate by weight. The potency of each capsule is not less than 50,000 units. Its moisture content is not more than 4.0 percent. The penicillin used conforms to the requirements prescribed by § 146a.24(a) for potassium penicillin except § 146a.24(a), (2) and (4). The pectin hydrolysate is obtained by mild hydrolysis of pectin with sodium hydroxide and hydrochloric acid. It is a free flowing and opalescent solution light tan to beige in color and is precipitated by the lower alcohols and ketones. Its pH is 6.0 to 7.0. It is substantially free of any turbidity or undissolved material. The pectin used conforms to the standards prescribed by the N. F. The sodium citrate and the sodium hydroxide and hydrochloric acid used in the preparation of the pectin hydrolysate conform to the standards prescribed therefor by the U.S.P.

(b) *Packaging.* Unless each capsule of buffered penicillin with pectin hydrolysate is enclosed in foil or plastic film and such enclosure complies with the definition of a tight container as prescribed by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the capsules by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The number of capsules in the immediate container is such that the total number of units therein is not less than 300,000.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of capsules in such batch, the number of capsules of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each capsule, the date on which the latest assay of the drug comprising such batch was completed, the batch mark and (unless submitted previously) the date on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency and average moisture of capsules collected during the time of capsuling the batch and, unless the capsules are packaged in dispensing-size containers immediately after they are capsuled, average moisture of capsules collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency and average moisture of capsules collected during each day the capsules are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity, and heat stability; and if it is crystalline penicillin G, penicillin G content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: One capsule for each 5,000 capsules in the batch, but in no case less than 30 capsules collected by taking single capsules at such intervals throughout the entire time of capsuling the batch that the quantities capsuled during the intervals are approximately equal;

(*b*) If, after capsuling, such person packages the batch into dispensing-size containers: 20 capsules, collected at equal intervals during each day the capsules are being packaged, except that this sample is not required if the capsules are packaged immediately after they are capsuled;

or

(*c*) If the person who requests certification is not the manufacturer of the batch (for the purpose of certification, a batch shall be that number of capsules filled by such person into dispensing-size containers during each day's packaging operations): One capsule for each 5,000 capsules in the batch, but in no case less than 30 capsules collected by taking single capsules at such intervals throughout each day of packaging the capsules that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; ten packages containing approximately equal portions of not less than 60 milligrams each, packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, one package of approximately 250 cc. of the pectin hydrolysate and one package of approximately five grams of the sodium citrate used in making the batch, one package of approximately 50 cc. of the hydrochloric acid, and one package of approximately five grams of the sodium hydroxide used in preparing the pectin hydrolysate.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or such sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of capsules buffered penicillin with pectin hydrolysate under the regulations in this part shall be:

(1) $0.75 for each capsule in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) and (*c*) of this section; $3.00 for the sample submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such capsules and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.39 Capsules procaine penicillin in oil.

(a) *Standards of identity, strength, quality, and purity.* Capsules procaine penicillin in oil are capsules composed of procaine penicillin, aluminum monostearate, and seasame oil or peanut oil, enclosed in a suitable and harmless soft gelatin capsule. The potency of each capsule is not less than 200,000 units. Its moisture content is not more than 2.5 percent. The procaine penicillin used conforms to the standards prescribed by § 146a.44(a), except § 146a.44(a) (2) and (3). Each other ingredient used, if its name is recognized in the U.S.P. or N.F. conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each capsule, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per capsule and average moisture.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH, penicillin K content (unless it is procaine penicillin G), crystallinity, and the procaine penicillin G content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; 1 capsule for each 5,000 capsules in the batch, but in no case less than 30 capsules, collected by taking single capsules at such intervals throughout the entire time of capsuling the batch that the quantities capsuled during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 10 packages each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146a.44 (b).

(iii) In case of an initial request for certification, the sesame oil or peanut oil and each other ingredient used in making the batch; 1 package of each containing, respectively, approximately 250 grams and approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $0.75 for each capsule in the sample submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such capsules and packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.40 Penicillin bougies (sodium penicillin bougies, calcium penicillin bougies, potassium penicillin bougies, procaine penicillin bougies, penicillin bougies sodium salt, penicillin bougies calcium salt, penicillin bougies potassium salt, penicillin bougies procaine salt).

(a) *Standards of identity, strength, quality, and purity.* Penicillin bougies are bougies composed of sodium penicillin, calcium penicillin, potassium penicillin, or procaine penicillin in an excipient of polyethylene glycol or of one or more other suitable and harmless diluents, binders, and lubricants. The potency of each bougie is not less than 25,000 units. Its moisture content is not more than 1.0 percent, except if it contains procaine penicillin, its moisture content is not more than 2.0 percent. The sodium penicillin, calcium penicillin, or potassium penicillin used conforms to the requirements of § 146a.24(a), except the limitation on penicillin K content and except § 146a.24(a) (1), (2), (3), and (4), but its potency is not less than 300 units per milligram. The procaine penicillin used conforms to the requirements of § 146a.44(a), except the limitation on penicillin K content and except § 146a.44(a) (2), (3), and (4). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each penicillin bougie is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the bougies by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor

changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of penicillin bougies shall bear, on its label or labeling as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark;

(ii) The number of units in each bougie of the batch;

(iii) The statement "Expiration date ----------," the blank being filled in, if crystalline penicillin or procaine penicillin is used without the addition of an excipient of polyethylene glycol, with the date which is 36 months; or if crystalline penicillin or procaine penicillin is used with the addition of an excipient of polyethylene glycol, with the date which is 24 months, or if crystalline penicillin or procaine penicillin is not used, with the date which is 12 months after the month during which the batch was certified.

(iv) If the excipient is polyethylene glycol, the statement "Store in refrigerator not above 15° C. (59° F.)", unless the person who requests certification has submitted to the Commissioner results of tests and assays showing that his drug is stable at room temperature;

(v) The statement "For veterinary use only."

(2) On the circular or other labeling within or attached to the package, if it is packaged for dispensing, adequate directions and warnings for the veterinary use of such drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of bougies in such batch, the number of bougies of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units in each bougie, the date on which the latest assay of the drug comprising such batch was completed, the date (unless submitted previously) on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency and average moisture of bougies collected during the time of making the batch, and, unless the bougies are packaged into dispensing-size containers immediately after they are made, average moisture of bougies collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency and average moisture of bougies collected during each day the bougies are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch; potency, moisture, pH, crystallinity, and heat stability if it is crystalline sodium or potassium penicillin, the penicillin G content if it is crystalline sodium or potassium penicillin G, and the procaine penicillin G content if it is crystalline procaine penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: One bougie for each 5,000 bougies in the batch, but in no case less than 30 bougies collected by taking single bougies at such intervals throughout the entire time of making the batch that the quantities made during the intervals are approximately equal.

(*b*) If, after making, such person packages the batch into dispensing-size containers: 20 bougies collected at equal intervals during each day the bougies are being packaged, except that this sample is not required if the bougies are packaged immediately after they are made; or

(*c*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of bougies filled by such person into dispensing-size containers during each day's packaging operations): One bougie for each 5,000 bougies in the batch, but in no case less than 30 bougies collected by taking single bougies at such intervals throughout each day of packaging the bougies that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 5 packages, or in the case of crystalline penicillin 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is not procaine penicillin and not less than 300 milligrams if it is procaine penicillin, packaged in accordance with the requirements of § 146a.24 (b) or § 146a.44 (b).

(iii) In case of an initial request for certification, each polyethylene glycol and each other ingredient used in making the batch; one package of each containing approximately 25 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin bougies under the regulations in this part shall be:

(1) $0.75 for each bougie in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) and (*c*) of this section; $3.00 for each sample submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such bougies and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.41 Crystalline penicillin and epinephrine in oil.

(a) *Standards of identity, strength, quality, and purity.* Crystalline penicillin and epinephrine in oil is a suspension of crystalline penicillin and epinephrine in a menstruum of refined peanut oil or sesame oil. Each milliliter has a potency of 300,000 units and contains 0.3 milligram of epinephrine. Its moisture content is not more than 0.2 percent. It is sterile. The penicillin used conforms to the requirements of § 146a.24 (a) for crystalline penicillin. The epinephrine, peanut oil, and sesame oil used conform to the standards prescribed therefor by the U.S.P.

(b) *Packaging.* The immediate container of crystalline penicillin and epinephrine in oil shall be of colorless transparent glass so closed as to be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that its contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The quantity of crystalline penicillin and epinephrine in oil in each such container shall be not less than one milliliter and not more than 20 milliliters unless it is packaged for repacking. Unless it is packaged for repacking each container shall be filled with a volume of crystalline penicillin and epinephrine in oil in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated whether administered in either single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date ----------," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its

label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of crystalline penicillin and epinephrine in oil shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that the epinephrine, peanut oil or sesame oil used in making such batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture and epinephrine content.

(ii) The penicillin used in making the batch; potency, sterility, toxicity, pyrogens, moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity, heat stability and the penicillin G content if it is crystalline penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one package for each 5,000 packages in the batch, but in no case less than 5 packages.

(*b*) For sterility testing; 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch:

(*a*) For all tests except sterility; 10 packages, each containing approximately equal portions of not less than 60 milligrams.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of not less than 300 milligrams.

Such samples shall be packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, the epinephrine and the peanut oil or sesame oil used in making the batch; one package of each containing approximately 2 grams and 250 grams, respectively.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of crystalline penicillin and epinephrine in oil under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii) (*a*), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examinations of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.42 Aluminum penicillin (aluminum penicillin salt).

(a) *Standards of identity, strength, quality, and purity.* Aluminum penicillin is the insoluble aluminum salt of a kind of penicillin or a mixture of two or more such salts, but the quantity of any salt of penicillin K therein is not more than 30 percent. Each such drug is so purified and dried that:

(1) Its potency is not less than 500 units per milligram;

(2) It is sterile;

(3) It is nonpyrogenic;

(4) It is nontoxic;

(5) Its moisture content is not more than 3 percent; and

(6) Its pH in saturated aqueous solution is not less than 3.5 and not more than 4.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of aluminum penicillin shall bear on its outside wrapper or container and the immediate container as hereinafter indicated, the following:

(1) The batch mark;

(2) The weight of the drug and the number of units in the immediate container;

(3) The statement "Expiration date _____", the blank being filled in with the date which is 12 months after the month during which the batch was certified.

(4) The statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)";

(5) The statement "For manufacturing use only";

(6) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of aluminum penicillin shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed with results of the tests and assays made by him on the batch for potency, sterility, pyrogens, toxicity, moisture, pH, and the penicillin K content.

(2) Such person shall submit in connection with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 6 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which aluminum penicillin is to be used, the manufacturer of a batch which is to be so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of each check test and assay as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) of this section.

(2) If the Commissioner considers that investigations, other than the examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.43 Aluminum penicillin in oil.

(a) *Standards of identity, strength, quality, and purity.* Aluminum penicillin in oil is a suspension of aluminum penicillin in a menstruum of refined peanut oil or sesame oil. Its potency is 300,000 units per milliliter. Its moisture content is not more than 1.5 percent. It is sterile. The aluminum penicillin used conforms to the requirements of § 146a.42(a). The peanut oil or sesame oil used conforms to the standards prescribed therefor by the U.S.P.

(b) *Packaging.* The immediate container of aluminum penicillin in oil shall be of colorless, transparent glass, so closed as to be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that its contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The quantity of aluminum penicillin in oil in each such container shall be not less than 1 milliliter and not more than 20 milliliters, unless it is packaged for repacking. Unless it is packaged for repacking, each container shall be filled with a volume of aluminum penicillin in oil in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated, whether administered in either single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter, (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(ii) On the outside wrapper or container, the statement "Store in refrigerator not above 15° C. (59° F.)."

(2) *It is packaged for dispensing and is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of aluminum penicillin in oil shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the aluminum penicillin used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that the peanut oil or sesame oil used in making such batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture.

(ii) The aluminum penicillin used in making the batch; potency, sterility, toxicity, pyrogens, moisture, pH, penicillin K content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one package for each 5,000 packages in the batch, but in no case less than 5 packages.

(*b*) For sterility testing; 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The aluminum penicillin used in making the batch:

(*a*) For all tests except sterility; 6 packages, each containing approximately equal portions of not less than 300 milligrams.

(*b*) For sterility testing: 10 packages, each containing approximately equal portions of not less than 300 milligrams.

Such samples shall be packaged in accordance with the requirements of § 146a.42 (b).

(iii) In case of an initial request for certification, the peanut oil or sesame oil used in making the batch; one package of each containing approximately 250 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of aluminum penicillin in oil under the regulations in this part shall be:

(1) $8.00 for each package in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) (*a*) and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than the examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.44 Procaine penicillin (penicillin procaine salt), procaine penicillin G (penicillin G procaine salt).

(a) *Standards of identity, strength, quality, and purity.* Procaine penicillin is the crystalline procaine salt of a kind of penicillin, or a mixture of two or more such salts prepared from procaine hydrochloride that complies with all the standards prescribed by the U.S.P., except for the color of the crystals and penicillin, but the quantity of any salt of penicillin K therein is not more than 30 percent; procaine penicillin G is procaine penicillin which contains not less than 85 percent by weight of the procaine salt of penicillin G. Each such drug is so purified and dried that:

(1) Its potency is not less than 900 units per milligram;

(2) It is sterile;

(3) It is nonpyrogenic;

(4) It is nontoxic;

(5) Its moisture content is not more than 4.2 percent; and

(6) Its pH in saturated aqueous solution is not less than 5 and not more than 7.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of procaine penicillin shall bear on its outside wrapper or container and the immediate container as hereinafter indicated, the following:

(1) The batch mark;

(2) The weight of the drug and the number of units in the immediate containers;

(3) The statement "Expiration date ----------," the blank being filled in with the date which is 36 months after the month during which the batch was certified, except that the blank may be filled in with the date which is 48 months or 60 months after the month during which the batch was certified, if the person who requests certification has submitted to the Commissioner results of

tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(4) The statement "For manufacturing use only";

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of procaine penicillin shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH, crystallinity, penicillin K content (unless it is procaine penicillin G), and the penicillin G content if it is procaine penicillin G.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which procaine penicillin is to be used, the manufacturer of a batch which is to be so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to each manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.45 Procaine penicillin in oil.

(a) *Standards of identity, strength, quality and purity.* Procaine penicillin in oil is a suspension of procaine penicillin in refined peanut oil or sesame oil, with or without the addition of one or more suitable and harmless dispersing agents and with or without the addition of a hardening agent. If it is intended solely for veterinary use and is conspicuously so labeled, it may contain nitrofurazone or adrenocorticotropic hormone (ACTH). Its potency is 300,000 units per milliliter, except if it is packaged and labeled solely for veterinary use. Its moisture content is not more than 1.4 percent. It is sterile, unless it is packaged and labeled solely for udder instillations of cattle or subcutaneous injection in fowl. The procaine penicillin used conforms to the requirements of § 146a.44 (a), except if the batch of procaine penicillin in oil is packaged and labeled solely for udder instillations of cattle, the penicillin used is exempt from the requirements of paragraph (a) (2), (3), and (4) of that section, or if the batch of procaine penicillin in oil is packaged and labeled solely for subcutaneous injection in fowl, the penicillin used is exempt from the requirements of paragraph (a) (2) and (3) of that section. The sesame oil and peanut oil used conform to the standards prescribed therefor by the U.S.P. The hardening agent is a refined hydrogenated and deodorized peanut oil free from rancidity; it has an iodine value of not more than 10; its free fatty acid content as oleic acid is not more than 1/10 of 1 percent, and its melting point is 64° C., ±2° C.

(b) *Packaging.* The immediate container of procaine penicillin in oil shall be of colorless transparent glass (unless it is packaged to contain a single dose), so closed as to be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, and shall be so sealed that its contents cannot be used without destroying such seal, except if it is labeled solely for udder instillations of cattle or subcutaneous injection in fowl it may be packaged in plastic or collapsible tubes which shall be well-closed containers as defined by the U. S. P. The immediate container shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limitation therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good marketing, storage, and distribution practice shall be disregarded. The quantity of procaine penicillin in oil in each such container shall be not less than 1 milliliter and not more than 20 milliliters, unless it is packaged for repacking or is packaged and labeled solely for veterinary use. Unless it is packaged for repacking, each such container shall be filled with a volume of procaine penicillin in oil in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated, whether administered in single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in, if it is packaged in plastic containers, with the date that is 12 months, or if its container is not plastic, with the date that is 36 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, or 36 months if the container is plastic or 48 months or 60 months if the container is not plastic, after the month during which the batch was certified, if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) On the outside wrapper or container and the immediate container, the statement "Shake well," if it does not contain a hardening agent.

(2) *It is packaged for dispensing and intended solely for veterinary use.* (i) If it does not contain adrenocorticotropic hormone, it shall comply with subparagraph (1) of this paragraph, except in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include adequate directions and warnings for the veterinary use of the drug by the laity, including a statement, if it is intended for subcutaneous injection in fowl, that it should be injected in the neck immediately behind the head.

(ii) If it contains adrenocorticotropic hormone, it shall comply with § 1.106(c) of this chapter and with the requirements of subparagraph (1) of this paragraph.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of procaine penicillin in oil shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the procaine penicillin used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that each ingredient used in making such batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility (unless it is intended solely for udder instillations of cattle or subcutaneous injection in fowl), and moisture.

(ii) The procaine penicillin used in making the batch; potency, toxicity, (unless it is intended for udder instillations of cattle) moisture, pH, crystallinity, penicillin K content (unless it is crystalline penicillin G), procaine penicillin G content if it is procaine penicillin G, and, unless the batch of procaine penicillin in oil is intended solely for udder instillations of cattle or subcutaneous injection in fowl, sterility or pyrogens.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch.

(*a*) For all tests except sterility; one package for each 5,000 packages in the batch, but in no case less than 5 packages.

(*b*) For sterility testing; 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The procaine penicillin used in making the batch:

(*a*) For all tests except sterility; 10 packages, each containing approximately equal portions of 300 milligrams.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of 300 milligrams.

Such samples shall be packaged in accordance with the requirements of § 146a.44 (b).

(iii) In case of an initial request for certification, the peanut oil or sesame oil and each dispersing and hardening agent or other ingredient used in making the batch; one package of each containing, respectively, approximately 250 grams and 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch of procaine penicillin in oil under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii) (*a*), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (b) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) (b) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.46 Crystalline penicillin for inhalation therapy.

(a) *Standards of identity, strength, quality, and purity.* Crystalline penicillin for inhalation therapy is crystalline sodium penicillin, potassium penicillin, or procaine penicillin, with or without one or more suitable and harmless diluents. Its moisture content is not more than 1.5 percent if it is crystalline sodium or potassium penicillin, and not more than 4.2 percent if it is procaine penicillin. The crystalline penicillin used conforms to the requirements of § 146a.24(a) except subparagraphs (2) and (4) of that paragraph. The procaine penicillin used conforms to the requirements of § 146a.44(a), except subparagraphs (2) and (3) of that paragraph. Each diluent used, if its name is recognized in the U.S.P. or N.F. conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container of crystalline penicillin for inhalation therapy shall be a tight container as defined by the U. S. P.; its closure shall be one through which a hypodermic needle cannot be introduced; and the container shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not less than 50,000 units and each may be packaged in combination with a container of the solvent, distilled water U. S. P., physiological salt solution U. S. P., physiological salt solution with the preservative chlorobutanol, or a solution of propylene glycol in distilled water.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date _____," the blank being filled in, if crystalline sodium penicillin or potassium penicillin is used, without a diluent, with the date that is 36 months, or if procaine penicillin is used, without a diluent, with the date that is 24 months, or if a diluent is used, with the date that is 18 months after the month during which the batch was certified.

(2) If it is packaged in combination with a container of a solvent, the statement "*Warning*—Not for injection."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of crystalline penicillin for inhalation therapy shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each immediate container, the quantity of each diluent used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each diluent used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity if it is crystalline penicillin, heat stability if it is crystalline sodium or potassium penicillin, the penicillin G content if it is crystalline sodium or potassium penicillin G, and the procaine penicillin G content if it is procaine penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers collected by taking single immediate containers, before or after labeling at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is not procaine penicillin, and not less than 300 milligrams if it is procaine penicillin, packaged in accordance with the requirements of § 146a.24 (b) or § 146a.44 (b).

(iii) In case of an initial request for certification, each diluent used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.47 Procaine penicillin for aqueous injection.

(a) *Standards of identity, strength, quality, and purity.* Procaine penicillin for aqueous injection is a dry mixture of procaine penicillin and one or more suitable and harmless suspending or dispersing agents, with or without one or more suitable and harmless preservatives and buffer substances, or it is an aqueous suspension of procaine penicillin and one or more suitable and harmless suspending or dispersing agents, buffer substances, and preservatives, except that preservatives are not required if the immediate container is packaged to contain a single dose and is conspicuously so labeled. If it is an aqueous suspension of the drug, it may contain procaine hydrochloride in a concentration not exceeding 2.0 percent, one or more suitable and harmless stabilizing agents, and, if it is intended solely for veterinary use, it may contain cortisone or a suitable derivative of cortisone. It is so purified that:

(1) If it is an aqueous suspension of the drug, each container or each milliliter shall contain not less than 300,000 units;

(2) It is sterile;

(3) If it is the dry mixture of the drug, its moisture content is not more than 4.2 percent;

(4) It is nonpyrogenic;

(5) It is nontoxic; and

(6) Its pH in saturated aqueous solution is not less than 5.0 and not more than 7.5.

The procaine penicillin used conforms to the requirements of § 146a.44 (a). Each other substance, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless, transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness, unless it is the aqueous suspension of the drug and it is packaged to contain a single dose. If it is the dry mixture of the drug, each such container shall contain 300,000 units, 600,000 units, 900,000 units, 1,200,000 units, 1,500,000 units, or 3,000,000 units, unless it is intended solely for veterinary use and it is conspicuously so labeled. Each such container may be packaged in combination with a container of a suitable aqueous diluent. If it is the aqueous suspension of the drug, each such container shall contain not less than 1 milliliter (unless it is packaged to contain a single dose) and not more than 12 milliliters (unless it is intended solely for veterinary use and is conspicuously so labeled), and each shall be filled with a volume in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated, whether administered in either single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____;" the blank being filled in, if it is a dry mixture of the drug, with the date that is 36 months, or if it is the aqueous suspension of the drug, with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 48 months or 60 months if it is the dry mixture of the drug, and 18 months, 24 months, 36 months, or 48 months if it is the aqueous suspension of the drug, after the month during which the batch was certified, if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) On the immediate container, if it is a dry mixture of the drug, the conditions under which suspensions made from such drug should be stored, and the statement "Sterile suspension may be kept at room temperature for 1 week, or in a refrigerator for 3 weeks, without significant loss of potency," unless this information is contained in the circular or other labeling within or attached to the package.

(iii) On the outside wrapper or container, if it is the aqueous suspension of the drug, the statement "Store in refrigerator not above 15° C. (59° F.)," unless the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him complies with standards prescribed by paragraph (a) of this section after having been stored at room temperature.

(iv) If it contains cortisone or a derivative of cortisone, after the name "procaine penicillin for aqueous injection," wherever it appears, the words "with _____," in juxtaposition with such name, the blank being filled in with the common or usual name of such ingredient.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the following requirements:

(i) If it does not contain cortisone or a derivative of cortisone, it shall comply with subparagraph (1) of this paragraph, except in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(ii) If it contains cortisone or a derivative of cortisone, the label and labeling of each package shall conform with the requirements prescribed by § 1.106(c) of this chapter and with the requirements of subparagraph (1) of this paragraph.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of procaine penicillin for aqueous injection shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the procaine penicillin used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section. If such batch, or any part thereof, is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture, pyrogens, toxicity, pH.

(ii) The procaine penicillin used in making the batch; potency, crystallinity, penicillin K content (unless it is procaine penicillin G), and the penicillin G content if it is procaine penicillin G.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(a) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(b) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The procaine penicillin used in making the batch; 3 packages containing approximately equal portions of not less than 500 milligrams each, packaged in accordance with the requirements of § 146a.44 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch of procaine penicillin for aqueous injection which is to be packaged in combination with an aqueous diluent which is not recognized by the U. S. P., or when any change is made in the composition of such diluent, five packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages

Each such package shall contain not less than approximately 300 milligrams taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), (iii), (iv), and (4) (i) of this section.

(2) $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (4) (ii) of this section.

(3) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.48 Ephedrine penicillin (penicillin ephedrine salt), ephedrine penicillin G (penicillin G ephedrine salt).

(a) *Standards of identity, strength, quality, and purity.* Ephedrine penicillin is the crystalline ephedrine salt of a kind of penicillin, or a mixture of two or more such salts prepared from ephedrine U. S. P. and penicillin, but the quantity of any salt of penicillin K therein is not more than 30 percent; ephedrine penicillin G is ephedrine penicillin which contains not less than 85 percent by weight of the ephedrine salt of penicillin G. Each such drug is so purified and dried that:

(1) Its potency is not less than 1,000 units per milligram;

(2) It is sterile;

(3) It is nontoxic;

(4) It is nonpyrogenic;

(5) Its moisture content is not more than 1.5 percent;

(6) Its pH in aqueous solution of 30 milligrams per milliliter is not less than 5 and not more than 7.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of ephedrine penicillin shall bear on its outside wrapper or container and the immediate container as hereinafter indicated, the following:

(1) The batch mark;

(2) The weight of the drug and the number of units in the immediate container;

(3) The statement "Expiration date ----------", the blank being filled in with the date which is 12 months after the month during which the batch was certified.

(4) The statement "For manufacturing use only;"

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Requests for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of ephedrine penicillin shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH, crystallinity, penicillin K content (unless it is ephedrine penicillin G), and the penicillin G content if it is ephedrine penicillin G.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from a different part of such bath, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with the contemplated requests for certification of batches of another drug in the manufacture of which ephedrine penicillin is to be used, the manufacturer of a batch which is to be so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to each manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed under subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.49 Ephedrine penicillin tablets.

(a) *Standards of identity, strength, quality, and purity.* Ephedrine penicillin tablets are tablets composed of ephedrine penicillin and one or more buffer substances, with or without one or more suitable and harmless diluents, binders, and lubricants. The potency of each tablet is not less than 30,000 units. Its moisture content is not more than 1.5 percent. When a tablet is dissolved as directed the potency of such solution is not less than 4,000 units per milliliter after it has been kept for one day at a temperature of 15° C. (59° F). Such solution is isotonic, and has a pH of 6.0, ±0.2. The ephedrine penicillin used conforms to the requirements of § 146a.48 (a) for ephedrine penicillin except subparagraphs (2) and (4) of § 146a.48 (a). Each buffer substance and preservative used, if their names are recognized in the U.S.P. or N.F., conform to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each tablet is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U.S.P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and

unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date ----------," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) A statement giving the method of dissolving the tablets, and a statement that distilled water U.S.P. should be used.

(iii) The conditions under which the solution should be stored, including a reference to its instability when stored under other conditions, and a statement "Prepare a fresh solution each 24 hours."

(iv) The statement "*Warning*—Not for injection or oral use."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying to the requirements of § 146.2 of this chapter, a person who requests certification of a batch of ephedrine penicillin tablets shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the ephedrine penicillin used in making such batch was completed, the number of units in each tablet, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising the batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per tablet and average moisture.

(ii) The ephedrine penicillin used in making the batch; potency, toxicity, moisture, pH, penicillin K content (unless it is ephedrine penicillin G), crystallinity, and the penicillin G content if it is ephedrine penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets, collected by taking single tablets at such intervals throughout the entire time of tableting that the quantities tableted during the intervals are approximately equal.

(ii) The ephedrine penicillin used in making the batch; six packages, each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146a.48 (b).

(iii) In case of an initial request for certification, each buffer substance, diluent, binder, and lubricant used in making the batch; one package of each, each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for services rendered with respect to each batch of ephedrine penicillin tablets under the regulations in this part shall be:

(1) $0.75 for each tablet in the sample submitted in accordance with paragraph (d) (3) (i) of this section, $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such tablets and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.50 Procaine penicillin and buffered crystalline penicillin for aqueous injection.

Procaine penicillin and buffered crystalline penicillin for aqueous injection conforms to all requirements prescribed by § 146a.47 for the dry mixture of procaine penicillin for aqueous injection, and is subject to all procedures prescribed by § 146a.47 for the dry mixture of procaine penicillin for aqueous injection, except that:

(a) Each immediate container shall contain not less than 50,000 units of buffered crystalline penicillin for each 300,000 units of procaine penicillin. The buffered crystalline penicillin conforms to the requirements prescribed by § 146a.37.

(b) If it is packaged as a single dose and its immediate container has two compartments separated by a tight rubber seal, one compartment shall contain an aqueous suspension of procaine penicillin which conforms to all requirements and procedures prescribed by § 146a.47 and one compartment shall contain the dry buffered crystalline penicillin.

(c) The circular or other labeling within or attached to the package, if it is packaged for dispensing, shall bear, in lieu of the statement prescribed by § 146a.47(c) (1) (ii), the statement "Sterile suspension may be kept in refrigerator for _____ week(s) without significant loss of potency," the blank being filled in with the figure "1," or if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him does not lose significant potency after having been stored in a refrigerator for 4 weeks, the blank may be filled in with the figure "4," unless it is packaged to conform with paragraph (b) of this section.

(d) In addition to complying with the requirements of § 146a.47 (d), a person who requests certification of a batch of procaine penicillin and buffered crystalline penicillin for aqueous injection shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the buffered crystalline penicillin used in making the batch for potency, crystallinity, heat stability, penicillin K content (unless it is buffered crystalline penicillin G) and the penicillin G content if it is buffered crystalline penicillin G, the number of units of procaine penicillin and the number of units of buffered crystalline penicillin in each immediate container of the batch. He shall also submit in connection with his request a sample consisting of three packages containing approximately equal portions of not less than 250 milligrams each of the buffered crystalline penicillin used in making the batch. If such batch is packaged for repacking, each portion in the sample required by § 146a.47 (d) (4) shall consist of approximately 400 milligrams in lieu of 300 milligrams.

(e) The fees for the services rendered with respect to the samples submitted under the regulations in this section shall be:

(1) $5.00 for each immediate container in the samples submitted in accordance with § 146a.47 (d) (3) (i) (a) and (4) (i).

(2) $4.00 for each immediate container of buffered crystalline penicillin submitted in accordance with the requirements of paragraph (d) of this section.

§ 146a.51 Buffered penicillin powder, penicillin powder with buffered aqueous diluent.

(a) *Standards of identity, strength, quality, and purity.* Buffered penicillin powder is a mixture of crystalline penicillin or procaine penicillin and suitable buffer substances, with or without probenecid, sodium salicylate and a suitable antihistaminic agent, with or without one or more suitable sulfonamides, and with or without the addition of one or more suitable and harmless diluents, colorings, and flavorings. Penicillin powder with buffered aqueous diluent is a packaged combination of one immediate container of crystalline penicillin or procaine penicillin, with or without suitable and harmless diluents, and one immediate container of an aqueous diluent containing suitable buffer sub-

stances and suitable and harmless preservatives, colorings, and flavorings. Its moisture content is not more than 1.0 percent, except if it contains procaine penicillin its moisture content is not more than 2.0 percent. The crystalline penicillin used conforms to the requirements of § 146a.24 (a) for crystalline penicillin, except subparagraphs (2) and (4) of that paragraph. The procaine penicillin used conforms to the requirements of § 146a.44 (a), except subparagraphs (2) and (3) of that paragraph. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container of buffered penicillin powder shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each immediate container may be packaged in combination with a container of a suitable and harmless aqueous vehicle, with or without probenecid, and with or without one or more suitable sulfonamides.

(c) *Labeling*—(1) *It is packaged for dispensing and is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter, (regulations issued under section 502(f) of the act), each package shall bear on its label and labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) A statement giving the method of dissolving the penicillin, if it is a packaged combination of one immediate container of buffered penicillin powder or penicillin powder and one immediate container of a vehicle.

(*b*) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months after the month during which the batch was certified if it is crystalline penicillin with no other ingredients; or the blank may be filled in with the date that is 48 months or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(c) The name of each buffer substance used in making the batch.

(ii) On the label and labeling if it contains, in addition to penicillin, one or more of the other active ingredients specified in paragraph (a) of this section, after the name "buffered penicillin powder," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of each such other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of buffered penicillin powder shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each immediate container, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; if buffered penicillin powder or penicillin powder with diluents: potency and moisture; if penicillin powder with no other ingredients: potency toxicity, moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity, heat stability if it is crystalline sodium or potassium penicillin, the penicillin G content if it is crystalline sodium or potassium penicillin G, and the procaine penicillin G content if it is procaine penicillin G.

(ii) If buffered penicillin powder or penicillin powder with diluents, the penicillin used in making the batch; potency, toxicity, moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity, heat stability if it is crystalline sodium or potassium penicillin, the penicillin G content if it is crystalline sodium or potassium penicillin G, and the procaine penicillin G content if it is procaine penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If it contains only penicillin and the penicillin used has been previously submitted, or it contains penicillin and other ingredients; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers.

(*b*) If it contains only penicillin and the penicillin has not been previously submitted; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 10 immediate containers or more than 17 immediate containers.

Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) If buffered penicillin powder or penicillin powder with diluents, the penicillin used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is not procaine penicillin, and not less than 500 milligrams if it is procaine penicillin, packaged in accordance with the requirements of § 146a.24(b) or § 146a.44(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch of buffered penicillin powder which is to be packaged in combination with an aqueous vehicle, or when any change is made in the composition of such aqueous vehicle; 5 packages of the vehicle included in the combination.

(4) No result referred to in subparagraph (2)(ii) of this paragraph, and no sample referred to in subparagraph (3)(ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of buffered penicillin powder under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d)(3)(i), (ii), (iii), and (iv) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

(f) *Exemption of buffered penicillin powder and penicillin powder with buffered aqueous diluent for veterinary use from certification.* Buffered penicillin powder and penicillin powder with buffered aqueous diluent that conform to the requirements of paragraphs (a) (except that they may contain one or more essential vitamin and mineral substances for nutritive purposes), (b), and (c) of this section shall be exempt from the requirements of sections 502(l) and 507 of the act, if they comply with all the following conditions:

(1) They are intended solely for veterinary use and are conspicuously so labeled.

(2) If they contain added vitamins or minerals, the labels bear the name and

quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear an expiration date that is not more than 36 months after the month during which the batch was last assayed and released by the manufacturer.

(4) The labels bear a statement that solutions prepared with the drugs are stable for not more than 24 hours.

(5) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Chronic respiratory disease (air-sac infection) in chickens.

(ii) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(iii) Infectious sinusitis in poultry.

(iv) As an aid in reducing the incidence and severity of bloat in cattle on legume pastures: *Provided*, That:

(*a*) The drug is intended to be administered in water or feed, and when used as directed in its labeling each animal receives not less than 75,000 units of penicillin per day; or

(*b*) The drug is a mixture of procaine penicillin and sodium chloride that contains not less than 793,000 units of penicillin per pound; its moisture content is not more than 0.1 percent if granulated salt is used and not more than 0.25 percent if rock salt is used; it is intended for administering on a continuous "free choice" basis; and its labeling bears information that not more than 2 days' supply of the drug shall be put before cattle at one time, after which the unused portion shall be discarded and replaced by a fresh supply.

§ 146a.52 Procaine penicillin and crystalline penicillin in oil.

(a) Procaine penicillin and crystalline penicillin in oil conforms to all requirements prescribed by § 146a.45 for procaine penicillin in oil, and is subject to all procedures prescribed by § 146a.45 for procaine penicillin in oil, except that:

(1) It contains not less than 50,000 units of crystalline penicillin for each 300,000 units of procaine penicillin, except if it is packaged and labeled solely for veterinary use. The crystalline penicillin used conforms to the requirements prescribed therefor by § 146a.24 (a), except if the batch of procaine penicillin and crystalline penicillin in oil is intended solely for udder instillations of cattle, the crystalline penicillin used is exempt from the requirements of paragraph (a) (2), (3), and (4) of that section.

(2) [Reserved.]

(3) In addition to complying with the requirements of § 146a.45 (d), a person who requests certification of a batch of procaine penicillin and crystalline penicillin in oil shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the crystalline penicillin G used in making the batch for potency, toxicity (unless it is intended for udder instillations of cattle), moisture, pH, penicillin K content (unless it is crystalline penicillin G), crystallinity, heat stability, the penicillin G content if it is crystalline penicillin G, and, unless the batch of procaine penicillin and crystalline penicillin in oil is intended solely for udder instillations of cattle, sterility and pyrogens; the number of units of procaine penicillin and the number of units of crystalline penicillin in each milliliter of the batch. In addition to the 10 immediate containers required by § 146a.45(d)(3)(i)(*b*), he shall also submit in connection with his request a sample consisting of not less than 6 packages of the batch of procaine penicillin and crystalline penicillin in oil and a sample of the crystalline penicillin used in making the batch, consisting of 10 packages, each containing approximately equal portions of not less than 60 milligrams, and 10 packages, each containing approximately equal portions of not less than 300 milligrams.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(1) $5.00 for each immediate container of the batch.

(2) $4.00 for each 60-milligram package of crystalline penicillin submitted in accordance with paragraph (a) (3) of this section.

(3) $10.00 for the 300-milligram packages submitted in accordance with paragraph (a) (3) of this section.

§ 146a.53 Capsules penicillin and novobiocin.

(a) *Standards of identity, strength, quality, and purity.* Capsules penicillin and novobiocin are crystalline penicillin G sodium or potassium and crystalline monosodium novobiocin, with or without one or more suitable and harmless buffer substances, lubricants, colorings, and flavorings, enclosed in a suitable and harmless gelatin capsule. Each capsule contains not less than 125,000 units of penicillin and not less than 125 milligrams of novobiocin. The moisture content is not more than 4.0 percent. The crystalline penicillin G used conforms to the requirements of § 146a.24 (a), except § 146a.24 (a) (2) and (4). The crystalline monosodium novobiocin used is produced by the growth of Streptomyces niveus, has a potency of not less than 750 micrograms per milligram, is nontoxic, has a moisture content of not more than 6.0 percent, and the pH in a saturated aqueous solution is not less than 6.5 and not more than 8.5. Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees.* Capsules penicillin and novobiocin conform to all requirements and procedures prescribed for crystalline penicillin G tablets by § 146a.27 (b), (c), (d), and (e), except with respect to disintegration time, and except that:

(1) The expiration date shall be the date that is 18 months after the month during which the batch was certified, except that if the person who requests certification has submitted to the Commissioner results of tests and assays that show such drug as prepared by him is stable for 24 months, 36 months, or 48 months, such date may be used for such drug.

(2) In addition to complying with the requirements of § 146a.27 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the novobiocin used in making the batch for potency, toxicity, pH, moisture, and crystallinity. He shall also submit in connection with his request (unless previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the novobiocin used in making the batch.

(3) The fees for the services rendered in accordance with the requirements of subparagraph (2) of this paragraph shall be:

(i) $1.00 for each capsule submitted in accordance with the requirements of § 146a.27(d)(3)(i)(*a*) (*1*) and (3).

(ii) $4.00 for each immediate container of novobiocin submitted.

§ 146a.54 Penicillin-streptomycin ointment (penicillin-streptomycin mineral oil suspension); penicillin-dihydrostreptomycin ointment (penicillin-dihydrostreptomycin mineral oil suspension).

(a) Penicillin-streptomycin ointment and penicillin-dihydrostreptomycin ointment conform to all requirements prescribed by § 146a.26 for penicillin ointment, execpt paragraph (c)(1)(ii) of that section, and are subject to all procedures prescribed by § 146a.26 for penicillin ointment, except that:

(1) It contains not less than 2,000 units of one or more kinds of penicillin salt per gram.

(2) It contains not less than 10 milligrams of streptomycin or dihydrostreptomycin per gram, unless it is intended solely for veterinary use and is conspicuously so labeled. If the ointment is intended for human use, the streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.101 (a) or § 146b.103 of this chapter, except the standards for sterility, toxicity, pyrogens, and histamine. If the ointment is intended solely for veterinary use, the streptomycin or dihydrostreptomycin used may conform to the standards prescribed by § 146b.114 (a) of this chapter.

(3) If it is intended solely for veterinary use and is conspicuously so labeled, it may contain cortisone or a suitable derivative of cortisone, a suitable and harmless salt of cobalt, one or more sulfonamides, and one or more suitable and harmless preservatives; if it is packaged and labeled solely for udder instillations of cattle it may contain papain; and if it is packaged and labeled solely for use as an aid in the treatment of Vibrio fetus in carrier bulls, or for intrauterine infusion in cows, it may contain 20 milli-

grams of diethylstilbestrol per dose as recommended in its labeling.

(b) If it is intended solely for veterinary use and it contains diethylstilbestrol, the labeling of each package shall conform to the requirements of § 1.106(c) of this chapter and to the requirements of § 146a.26(c)(1)(i).

(c) In addition to complying with the requirements of § 146a.26 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate. He shall also submit in connection with his request a sample consisting of not less than six packages, or if it contains two or more kinds of penicillin salt, seven packages, of such ointment and (unless it was previously submitted) a sample consisting of six packages containing approximately equal portions of not less than 0.5 gram each of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(d) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (c) of this section shall be:

(1) $5.00 for each immediate container of the ointment.

(2) $4.00 for each immediate container of streptomycin or dihydrostreptomycin.

§ 146a.55 Penicillin-streptomycin bougies; penicillin-dihydrostreptomycin bougies.

(a) Penicillin-streptomycin bougies and penicillin-dihydrostreptomycin bougies conform to all requirements prescribed by § 146a.40 for penicillin bougies, except paragraph (c)(1)(iv) of that section, and are subject to all procedures prescribed by § 146a.40 for penicillin bougies, except that:

(1) Each bougie contains not less than 25 milligrams of streptomycin or dihydrostreptomycin.

(2) In lieu of the directions prescribed for penicillin bougies by § 146a.40 (c)(1)(ii), each package shall bear on the outside wrapper or container and the immediate container the number of units of penicillin and the number of milligrams of streptomycin or dihydrostreptomycin in each bougie.

(3) In addition to complying with the requirements of § 146a.40 (d), a person who requests certification of a batch of penicillin-streptomycin bougies or penicillin-dihydrostreptomycin bougies shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, moisture, pH, and its streptomycin content if it is dihydrostreptomycin; the number of units of penicillin and the number of milligrams of streptomycin or dihydrostreptomycin in each bougie of the batch. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of six packages containing approximately equal portions of not less than 0.5 gram each of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(b) The fees for the services rendered in accordance with the requirements of paragraph (a) (3) of this section shall be:

(1) $1.00 for each bougie submitted in accordance with the requirements of § 146a.40(d)(3)(i)(*a*) and (*c*).

(2) $4.00 for each immediate container of streptomycin or dihydrostreptomycin.

§ 146a.56 Penicillin-bacitracin ointment.

(a) Penicillin-bacitracin ointment conforms to all requirements prescribed by § 146a.26 for penicillin ointment and is subject to all procedures prescribed by § 146a.26 for penicillin ointment, except that:

(1) It contains not less than 2,000 units of penicillin per gram;

(2) It contains not less than 500 units of bacitracin per gram; the bacitracin used conforms to the standards prescribed therefor by § 146e.401(a) of this chapter, except paragraph (a) (2), (3), (4), and (8) of that section;

(3) [Reserved.]

(4) In addition to complying with the requirements of § 146a.26(d) a person who requests certification of a batch of penicillin-bacitracin ointment shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and date of the latest tests and assays of the bacitracin used in making the batch for potency, moisture, and pH, and ash content. He shall also submit in connection with his request a sample consisting of not less than six packages of penicillin-bacitracin ointment and (unless it was previously submitted) a sample consisting of six packages containing approximately equal portions of not less than 0.5 gram each of the bacitracin used in making the batch, packaged in accordance with the requirements of § 146e.401 (b) of this chapter.

(b) The fees for the services rendered in accordance with the requirements of paragraph (a) (4) of this section shall be:

(1) $5.00 for each immediate container of ointment submitted.

(2) $4.00 for each immediate container of bacitracin submitted.

§ 146a.57 Procaine penicillin and streptomycin in oil; procaine penicillin and dihydrostreptomycin in oil.

(a) Procaine penicillin and streptomycin in oil and procaine penicillin and dihydrostreptomycin in oil conform to all requirements and to all procedures prescribed in § 146a.45 for procaine penicillin in oil for udder instillations of cattle or subcutaneous injection in fowl, except that:

(1) It contains not less than 2.0 milligrams of streptomycin or dihydrostreptomycin per milliliter. The streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.101 (a) or § 146b.103 of this chapter, except the standards for sterility, pyrogens, and histamine, or by § 146b.114 (a) of this chapter, except that if it is intended for udder instillations of cattle the streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.101 (a) or § 146b.106 of this chapter, except the standards for sterility, toxicity, pyrogens, and histamine, or by § 146b.114 (a) of this chapter, except the standard for toxicity.

(2) It may contain cortisone or a suitable derivative of cortisone, a suitable and harmless salt of cobalt and/or one or more suitable sulfonamides and papain, if it is intended solely for udder instillations of cattle, each of which, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(3) In addition to the labeling requirements prescribed for procaine penicillin in oil by § 146a.45(c), each package shall bear on the outside wrapper or container and the immediate container the statement "For udder instillations of cattle only" or the statement "For subcutaneous injection in fowl only"; and if it is a multiple-dose container, the statement "Shake well." Each package shall also bear on its label and labeling, if it contains one or more of the other active ingredients specified in subparagraph (2) of this paragraph, after the name "procaine penicillin and streptomycin in oil" or "procaine penicillin and dihydrostreptomycin in oil," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of each such other ingredient)," in juxtaposition with such name.

(4) In addition to complying with the requirements of § 146a.45 (d), a person who requests certification of a batch of procaine penicillin and streptomycin in oil or procaine penicillin and dihydrostreptomycin in oil shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, toxicity, (if it is intended for subcutaneous injection in fowl), moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin; the number of units of penicillin and the number of milligrams of streptomycin or dihydrostreptomycin in each milliliter of the batch or in each prescribed dose. He shall also submit in connection with his request a sample consisting of not less than six immediate containers of the batch and (unless it was previously submitted) a sample consisting of six packages containing approximately

equal portions of not less than 0.5 gram each of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(b) The fees for the services rendered in accordance with the requirements of paragraph (a) (4) of this section shall be:

(1) $5.00 for each immediate container of the procaine penicillin and streptomycin or dihydrostreptomycin in oil submitted.

(2) $4.00 for each immediate container of streptomycin or dihydrostreptomycin used in making the batch.

§ 146a.58 Penicillin-streptomycin; penicillin-dihydrostreptomycin veterinary.

(a) *Standards of identity, strength, quality and purity.* Penicillin-streptomycin and penicillin-dihydrostreptomycin veterinary are procaine penicillin, crystalline sodium penicillin, potassium penicillin, *l*-ephenamine penicillin G, or diethylaminoethyl ester penicillin G hydriodide (if intended solely for veterinary use and conspicuously so labeled) or a mixture of two or more such salts and streptomycin sulfate or dihydrostreptomycin sulfate, with or without suitable and harmless buffer substances and suspending or dispersing agents. Each drug is sterile, nontoxic, and nonpyrogenic. Its moisture content is not more than 3.5 percent, except if it contains procaine penicillin its moisture content is not more than 4.2 percent. When prepared for injection as directed in its labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin used conforms to the requirements of § 146a.24(a), § 146a.44(a), § 146a.64(a), or § 146a.74(a). The streptomycin sulfate used conforms to the requirements prescribed for streptomycin sulfate by § 146b.101(a) of this chapter. The dihydrostreptomycin sulfate used conforms to the requirements prescribed for dihydrostreptomycin sulfate by § 146b.103 of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium. Penicillin-streptomycin is also the drug described in § 146a.84 of this chapter if it conforms to all requirements of that section and of § 141a.60 of this chapter, except that it contains streptomycin in lieu of a mixture of streptomycin and dihydrostreptomycin.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing it shall be in immediate containers of colorless (unless it is intended solely for veterinary use), transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Unless it is intended solely for veterinary use and is conspicuously so labeled or it is a single-dose container that contains not less than 300,000 units, each such container shall contain 300,000 units, 600,000 units, 900,000 units, 1,500,000 units, or 3,000,000 units of procaine penicillin, crystalline sodium penicillin, potassium penicillin, or *l*-ephenamine penicillin G and not less than 0.25 gram of streptomycin for each 300,000 units of penicillin, except that if it is a mixture of two salts of penicillin it shall contain not less than 100,000 units of crystalline sodium penicillin or potassium penicillin for each 300,000 units of procaine penicillin. Each such container may be packaged in combination with a container of a solvent consisting of water for injection U.S.P., dextrose injection U.S.P., or sodium chloride injection U.S.P.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 48 months after the month in which the batch was certified, except that the blank may be filled in with the date that is 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section, and except that in no case shall the blank be filled in with the date that is more than 24 months after the month in which the batch was certified if it contains diethylaminoethyl ester penicillin G hydriodide.

(2) *It contains diethylaminoethyl penicillin G hydriodide or dihydrostreptomycin.* The outside wrapper or container and the immediate container shall bear the statement "For veterinary use only."

(3) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with the requirements prescribed by subparagraphs (1) and (2) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(4) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The number of units of each salt of penicillin in each gram.

(ii) The number of milligrams of streptomycin or dihydrostreptomycin in each gram.

(iii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iv) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(v) The information required by subparagraph (1) (i) of this paragraph.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin and streptomycin or penicillin and dihydrostreptomycin veterinary shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the number of units of each salt of penicillin, and the number of grams of streptomycin or dihydrostreptomycin in each package, the batch marks, and (unless they were previously submitted) the dates on which the latest assays of the penicillin and streptomycin or dihydrostreptomycin used in making such batch were completed, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch and a statement that each such ingredient conforms to the requirements prescribed therefor by this section. If such batch, or any part thereof, is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, toxicity, pyrogens, moisture, pH.

(ii) The procaine penicillin used in making the batch; potency, crystallinity, penicillin K content (unless it is procaine penicillin G), and the penicillin G content if it is procaine penicillin G.

(iii) The crystalline sodium or potassium penicillin used in making the batch; potency, crystallinity, heat stability, penicillin K content unless it is crystalline penicillin G), and the penicillin G content if it is crystalline penicillin G.

(iv) The *l*-ephenamine penicillin G used in making the batch; potency, crystallinity, heat stability, penicillin G content, and specific rotation.

(v) The diethylaminoethyl ester penicillin G hydriodide used in making the batch; potency, crystallinity, and penicillin G content.

(vi) The streptomycin or dihydrostreptomycin used in making the batch; potency, histamine content, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if

such batch is packaged for dispensing, such person shall submit in connection with his request in the quantities hereinafter indicated accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 12 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The procaine penicillin used in making the batch; 3 packages containing approximately equal portions of not less than 0.5 gram each packaged in accordance with the requirements of § 146a.44 (b).

(iii) The crystalline penicillin used in making the batch; 3 packages containing approximately equal portions of not less than 250 milligrams each packaged in accordance with the requirements of § 146a.24 (b).

(iv) The *l*-ephenamine penicillin G used in making the batch; 3 packages containing approximately equal portions of not less than 0.5 gram each packaged in accordance with the requirements of § 146a.64 (b).

(v) The diethylaminoethyl ester penicillin G hydriodide used in making the batch; 3 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with § 146a.74(b).

(vi) The streptomycin or dihydrostreptomycin used in making the batch; 6 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(vii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility; 12 approximately equal portions of at least 2 grams.

(ii) For sterility testing; 10 approximately equal portions of at least 0.5 gram.

Each such portion shall be taken from a different part of such batch, and each shall be packaged in a separate container and in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii), (iii), (iv), (v), and (vi) of this paragraph and no samples referred to in subparagraph (3) (ii), (iii), (iv), (vi), and (vii) of this paragraph are required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), (v), (vi), and (vii) of this section; $5.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) (*a*) and (4) (i) of this section; $10.00 for all immediate containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (d) (4) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.59 Penicillin tooth powder (tooth powder with penicillin).

(a) *Standards of identity, strength, quality, and purity.* Penicillin tooth powder is a mixture of crystalline penicillin and one or more suitable cleansing and polishing substances, with or without suitable and harmless diluents, colorings, and flavorings. Its potency is 500 units per gram. Its moisture content is not more than 2.0 percent. The crystalline penicillin used conforms to the requirements of § 146a.24(a) for crystalline penicillin, except the limitation on penicillin K content and except subparagraphs (2) and (4) of that paragraph. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not more than 3 ounces.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin tooth powder shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH, crystallinity, heat stability, and the penicillin G content if it is crystalline sodium or potassium penicillin G.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146a.24 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin tooth powder under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146a.60 Penicillin-bacitracin troches; penicillin-zinc bacitracin troches.

(a) Penicillin-bacitracin troches and penicillin-zinc bacitracin troches conform to all the requirements prescribed by § 146a.30 for penicillin troches, and are subject to all procedures prescribed by § 146a.30 for penicillin troches, except paragraph (f) of that section, and except that:

(1) Each troche shall contain not less than 50 units of bacitracin or zinc bacitracin. The bacitracin used conforms to the standards prescribed by § 146e.401 (a) of this chapter, except § 146e.401 (a) (2), (4), and (8). The zinc bacitracin used conforms to the standards prescribed by § 146e.418 (a) of this chapter.

(2) [Reserved.]

(3) In addition to complying with the requirements of § 146a.30 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the bacitracin or zinc bacitracin used in making the batch for potency, toxicity, moisture, pH, ash content, if it is bacitracin, and zinc content, if it is zinc bacitracin. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 6 packages, each containing approximately equal portions of not less than 500 milligrams of the bacitracin (or not less than 1.0 gram of the zinc bacitracin) used in making the batch, packaged in accordance with the requirements of § 146e.401 (b) or § 146e.418 (b) of this chapter.

(b) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (a) (3) of this section shall be:

(1) $1.00 for each troche submitted in accordance with the requirements of § 146a.30 (d) (3) (i) (*a*) and (*c*).

(2) $4.00 for each immediate container of bacitracin or zinc bacitracin submitted.

§ 146a.61 Potassium penicillin V (potassium penicillin V salt).

(a) *Standards of identity, strength, quality, and purity.* Potassium penicillin V is the crystalline potassium salt of penicillin V. It contains not less than than 90 percent by weight of the potassium salt of penicillin V. It is so purified and dried that:

(1) Its potency is not less than 1,380 units per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 1.5 percent.

(4) Its pH in a solution containing 30 milligrams per milliliter is not less than 4.0 and not more than 7.5.

(b) *Packaging; labeling; request for certification, samples; fees.* Proceed as directed in § 146a.103 (b), (c), (d), and (e).

§ 146a.62 Penicillin-neomycin ointment.

Penicillin-neomycin ointment conforms to all requirements and is subject to all procedures prescribed by § 146a.26 for penicillin ointment, except that:

(a) It contains neomycin, and it may contain more than one salt of penicillin. The neomycin used conforms to the standards prescribed by § 146e.410 (a) (2) of this chapter, except the standard for toxicity.

(b) It may contain cortisone or a suitable derivative of cortisone.

(c) In addition to the labeling prescribed by § 146a.26(c), each package shall bear on the outside wrapper or container and the immediate container the statement "For udder instillation of cattle only." If it contains cortisone or a derivative of cortisone, each package shall bear on its label and labeling, after the name "penicillin-neomycin ointment," wherever it appears, the words "with _____," the blank being filled in with the common or usual name of such other ingredient, in juxtaposition with such name.

(d) In addition to complying with the requirements of § 146a.26 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, moisture, and pH; and the number of units of each kind of penicillin salt and the number of milligrams of neomycin in each gram of the batch. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making the batch.

(e) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (d) of this section shall be:

(1) $5.00 for each immediate container of ointment.

(2) $4.00 for each immediate container of the neomycin used in making the batch.

§ 146a.63 Crystalline penicillin and bacitracin.

(a) *Standards of identity, strength, quality, and purity.* Crystalline penicillin and bacitracin is composed of crystalline sodium penicillin or potassium penicillin and bacitracin with or without suitable and harmless buffer substances and dispersing agents. It is so purified and dried that:

(1) It is sterile;

(2) It is nontoxic;

(3) It is nonpyrogenic;

(4) Its moisture content is not more than 5.0 percent;

(5) The pH of an aqueous solution prepared as directed in its labeling is not less than 5.0 and not more than 7.5.

The crystalline penicillin used conforms to the standard prescribed by § 146a.24 (a). The bacitracin used conforms to the requirements prescribed by § 146e.401 (a) of this chapter. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practices shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness; each such container shall contain 1,500,000 units of crystalline penicillin and 60,000 units of bacitracin and each may be packaged in combination with a container of the solvent, water for injection U. S. P., physiological salt solution U. S. P., or with an aqueous solution of a suitable local anesthetic.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(ii) On the circular or other labeling within or attached to the package, the conditions under which such solutions should be stored, including a reference to their instability when stored under other conditions, and the statement "Sterile solution may be kept in refrigerator for 3 days without significant loss of potency."

(2) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container, the following:

(i) The number of units of crystalline penicillin per milligram and the number of grams in the immediate container.

(ii) The number of units of bacitracin per milligram and the number of grams in the immediate container.

(iii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iv) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(v) The information required by subparagraph (1) of this paragraph.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of crystalline penicillin and

bacitracin shall submit with his request a statement showing the batch mark, the number of packages in such batch, the number of units of penicillin and the number of units of bacitracin in each package, the batch marks, and (unless they were previously submitted) the dates on which the latest assays of the penicillin and bacitracin used in making such batch were completed, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch and a statement that each such ingredient conforms to the requirements prescribed therefor by this section. If such batch,, or any part thereof, is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following made by him on an accurately representative sample of:

(i) The batch; potency, sterility, toxicity, pyrogens, moisture, pH.

(ii) The crystalline penicillin used in making the batch; potency, crystallinity, heat stability, penicillin K content (unless it is crystalline penicillin G), and the penicillin G content if it is crystalline penicillin G.

(iii) The bacitracin used in making the batch; potency, toxicity, ash content, and heavy metals content.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request in the quantities hereinafter indicated accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The crystalline penicillin used in making the batch; 3 packages, each containing approximately equal portions of not less than 250 milligrams, packaged in accordance with the requirements of § 146a.24(b).

(iii) The bacitracin used in making the batch: 4 packages, each containing approximately 0.5 gram packaged in accordance with the requirements of § 146e.401(b) of this chapter.

(iv) In case of an initial request for certification, each other ingredient used in making the batch; 1 package of each containing approximately 5 grams.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility; 10 approximately equal portions of at least 2 grams each.

(ii) For sterility testing; 10 approximately equal portions of at least 0.5 gram each.

Each such portion shall be taken from different parts of such batch, and each shall be packaged in a separate container and in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) and (iii) of this paragraph, and no sample referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) (*a*) and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (4) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.64 *l*-Ephenamine penicillin G (penicillin G *l*-ephenamine salt).

(a) *Standards of identity, strength, quality and purity.* *l*-Ephenamine penicillin G is the heat stable crystalline *levo*-N-methyl-1, 2-diphenyl-2-hydroxyethylamine salt of penicillin G, prepared from crystalline penicillin G and crystalline dl-N-methyl-1, 2-diphenyl-2-hydroxyethylamine hydrochloride (98 percent purity and a melting point of 268.5° C. ±2.5° C.). It contains not less than 85 percent by weight of the *levo*-N-methyl-1, 2-diphenyl-2-hydroxyethylamine salt of penicillin G. It is so purified and dried that:

(1) Its potency is not less than 900 units per milligram;

(2) It is sterile;

(3) It is nonpyrogenic;

(4) It is nontoxic;

(5) Its moisture content is not more than 1.5 percent;

(6) Its pH in a saturated aqueous solution is not less than 5 and not more than 7.5; and

(7) Its specific rotation in water-acetone (1+1) at 20° C. is +125° ±5°.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container as hereinafter indicated, the following:

(1) The batch mark;

(2) The weight of the drug and the number of units in the immediate container;

(3) The statement "Expiration date ----------," the blank being filled in with the date which is 48 months after the month during which the batch was certified;

(4) The statement "For manufacturing use only";

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him for potency, sterility, toxicity, pyrogens, moisture, pH, crystallinity, heat stability, the penicillin G content, and specific rotation.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which it is to be used, the manufacturer of a batch which is to be so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drugs. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) of this section;

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.65 *l*-Ephenamine penicillin G in oil.

(a) *Standards of identity, strength, quality, and purity.* *l*-Ephenamine penicillin G in oil is a suspension of *l*-ephenamine penicillin G in refined peanut oil or sesame oil with or without the addition of one or more suitable and harmless dispersing agents. Its potency is 300,000 units per milliliter unless it is packaged and labeled solely for veterinary use. It is sterile. Its moisture content is not more than 1 percent. The *l*-ephenamine penicillin G used conforms to the requirements of § 146a.64 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container shall be of colorless transparent glass (unless it is packaged to contain a single dose), so closed as to be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, and shall be so sealed that the contents cannot be used without destroying such seal. The immediate container shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. If it is packaged for dispensing, each such container shall contain not less than 1.0 milliliter and not more than 20 milliliters and each shall be filled with a volume in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated, whether administered in single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the *l*-ephenamine penicillin G used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that each ingredient used in making such batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph such person shall submit in connection with his request results of tests and assays of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, and moisture.

(ii) The *l*-ephenamine penicillin G used in making the batch; potency, sterility, pyrogens, toxicity, moisture, pH, crystallinity, heat stability, penicillin G content, and specific rotation.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one package for each 5,000 packages in the batch, but in no case less than 5 packages.

(*b*) For sterility testing; 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The *l*-ephenamine penicillin G used in making the batch:

(*a*) For all tests except sterility; 10 packages, each containing approximately equal portions of not less than 300 milligrams.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of not less than 300 milligrams.

Each such portion shall be packaged in accordance with the requirements of § 146a.64 (b).

(iii) In case of an initial request for certification, one package containing approximately 150 grams of the peanut oil or sesame oil used and one package containing approximately 5 grams of each dispersing agent used.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii) (*a*), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.66 *l*-Ephenamine penicillin G for aqueous injection.

(a) *Standards of identity, strength, quality, and purity.* *l*-Ephenamine penicillin G for aqueous injection is a dry mixture of *l*-ephenamine penicillin G and one or more suitable and harmless suspending or dispersing agents, with or without one or more suitable and harmless preservatives and buffer substances, or it is an aqueous suspension of *l*-ephenamine penicillin G and one or more suitable and harmless suspending or dispersing agents, buffer substances, and preservatives, except that preservatives are not required if the immediate container is packaged to contain a single dose and is conspicuously so labeled. It is so purified that:

(1) If it is an aqueous suspension of the drug, each container or each milliliter shall contain not less than 300,000 units, unless it is packaged and labeled solely for veterinary use;

(2) It is sterile;

(3) If it is the dry mixture of the drug, its moisture content is not more than 1.5 percent;

(4) It is nonpyrogenic;

(5) It is nontoxic; and

(6) Its pH in saturated aqueous solution is not less than 5.0 and not more than 7.5.

The *l*-ephenamine penicillin G used conforms to the requirements of §146a.64 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the

strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness, unless it is the aqueous suspension of the drug and it is packaged to contain a single dose. If it is the dry mixture of the drug, each such container shall contain 300,000 units, 600,000 units, 900,000 units, 1,200,000 units, 1,500,000 units, or 3,000,000 units (unless it is packaged and labeled solely for veterinary use), and each may be packaged in combination with a container of a suitable aqueous diluent. If it is the aqueous suspension of the drug, each such container shall contain not less than 1 milliliter (unless it is packaged to contain a single dose) and not more than 10 milliliters (unless it is packaged and labeled solely for veterinary use), and each shall be filled with a volume in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated, whether administered in either single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in, if it is the dry mixture of the drug, with the date that is 18 months, or if it is the aqueous suspension of the drug, with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) On the outside wrapper or container, if it is the aqueous suspension of the drug, the statement "Store in refrigerator not above 15° C. (59°F.)" or "Store below 15° C. (59° F.)," unless the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section after having been stored at room temperature.

(iii) On the circular or other labeling within or attached to the package, if it is the dry mixture of the drug and is packaged for dispensing, the conditions under which suspensions made from such drug should be stored, and the statement "Sterile suspension may be kept at room temperature for 1 week or in refrigerator for 3 weeks, without significant loss of potency."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of *l*-ephenamine penicillin G for aqueous injection shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the *l*-ephenamine penicillin G used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section. If such batch, or any part thereof, is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: potency, sterility, moisture (unless it is the aqueous suspension of the drug), pyrogens, toxicity, pH.

(ii) The *l*-ephenamine penicillin G used in making the batch: potency, crystallinity, heat stability, penicillin G content, and specific rotation.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The *l*-ephenamine penicillin G used in making the batch; 3 packages containing approximately equal portions of not less than 500 milligrams each, packaged in accordance with the requirements of § 146a.64 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch, one package of each containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch which is to be packaged in combination with an aqueous diluent which is not recognized by the U. S. P., or when any change is made in the composition of such diluent; 5 packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (a), (ii), (iii), (iv), and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (4) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.67 Procaine penicillin in streptomycin sulfate solution; procaine penicillin in dihydrostreptomycin sulfate solution veterinary (procaine penicillin in crystalline dihydrostreptomycin sulfate solution veterinary).

(a) *Standards of identity, strength, quality, and purity.* Procaine penicillin in streptomycin sulfate solution is procaine penicillin suspended in an aqueous solution of streptomycin sulfate. Procaine penicillin in dihydrostreptomycin sulfate solution veterinary is procaine penicillin suspended in an aqueous solution of dihydrostreptomycin sulfate or crystalline dihydrostreptomycin sul-

fate. Such solution shall contain one or more suitable and harmless buffer substances, preservatives, and suspending or dispersing agents, and it may contain one or more suitable and harmless stabilizing agents and procaine hydrochloride in a concentration not exceeding 2 percent, and, if it is intended solely for veterinary use, it may contain a suitable antihistaminic, a suitable anticholinergic and cortisone, or a suitable derivative of cortisone. It is so purified that:

(1) Each milliliter shall contain not less than 100,000 units of procaine penicillin and not less than 0.25 gram of streptomycin sulfate or dihydrostreptomycin sulfate, but each immediate container shall contain not less than 300,000 units of procaine penicillin and not less than 0.25 gram of streptomycin sulfate or dihydrostreptomycin sulfate;

(2) It is sterile;

(3) It is nonpyrogenic;

(4) It is nontoxic; and

(5) Its pH is not less than 5.0 and not more than 8.0.

The procaine penicillin used conforms to the requirements prescribed by § 146a.44(a). The streptomycin sulfate used conforms to the requirements prescribed by § 146b.101(a) or § 146b.106(a) of this chapter. The dihydrostreptomycin sulfate used conforms to the requirements prescribed by § 146b.103(a) or § 146b.106(a) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless (unless it is intended solely for veterinary use) transparent glass closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness, unless it is packaged to contain a single dose. Each such container shall contain not less than 1 milliliter (unless it is packaged to contain a single dose) and not more than 30 milliliters (unless it is packaged and intended solely for veterinary use), and each shall be filled with a volume in excess of that designated, which excess shall be sufficient to permit the withdrawal and administration of the volume indicated, whether administered in either single or multiple doses.

(c) *Labeling*—(1) *It does not contain dihydrostreptomycin, it is packaged for dispensing, and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container, the statement "Store in refrigerator not above 15° C. (59° F.)."

(ii) On the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, or 24 months, or 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with the following requirements:

(i) If it does not contain an antihistaminic, an anticholinergic, or cortisone, or a derivative of cortisone, it shall comply with the requirements of subparagraph (1) of this paragraph, except in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include adequate directions and warnings for the veterinary use of the drug by the laity.

(ii) If it contains an antihistaminic, an anticholinergic, or cortisone or a derivative of cortisone, it shall comply with the requirements prescribed by § 1.106 (c) of this chapter and with the requirements of subparagraph (1) of this paragraph. Each package shall also bear on its label or labeling, the following:

(*a*) The statement "For use only in cats, dogs, and horses; not for use in horses to be slaughtered for human consumption."

(*b*) After the name "procaine penicillin in streptomycin sulfate solution," or "procaine penicillin in dihydrostreptomycin sulfate solution veterinary," wherever such name appears, the words "with _____," in juxtaposition with such name, the blank being filled in with the common or usual name of the antihistaminic, the anticholinergic, the cortisone, or the derivative of cortisone.

(3) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container, the following:

(i) The number of units of procaine penicillin and the number of milligrams or grams of streptomycin sulfate or dihydrostreptomycin sulfate in each milliliter.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The information required by subparagraph (1) (i) and (ii) of this paragraph.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the number of units of procaine penicillin and the number of milligrams or grams of streptomycin sulfate or dihydrostreptomycin sulfate in each milliliter of the batch, the batch marks and (unless they were previously submitted) the dates on which the latest assays of the procaine penicillin and streptomycin sulfate or dihydrostreptomycin sulfate used in making such batch were completed, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency, sterility, pH, and, if it does not contain a vegetable oil as a suspending agent, toxicity and pyrogens.

(ii) The procaine penicillin used in making the batch; potency (toxicity and pyrogens if it is used in making a batch containing a vegetable oil as a suspending agent), crystallinity, penicillin K content (unless it is procaine penicillin G), and the penicillin G content if it is procaine penicillin G.

(iii) The streptomycin sulfate or dihydrostreptomycin sulfate used in making the batch; potency (toxicity and pyrogens if it is used in making a batch containing a vegetable oil as a suspending agent), histamine content, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 12 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The procaine penicillin used in making the batch; three packages, or 10 packages if it is used to make a batch containing a vegetable oil as a suspending agent, each containing approximately equal portions of not less than

0.5 gram, packaged in accordance with the requirements of § 146a.44(b).

(iii) The streptomycin sulfate or dihydrostreptomycin sulfate used in making the batch; six packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146b.101(b) of this chapter. If the streptomycin or dihydrostreptomycin used in making the batch is a solution of the drug, the person who requests certification shall dry a sufficient quantity of the solution to meet these sample requirements.

(iv) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of:

(i) For all tests except sterility; 12 approximately equal portions of at least 2 milliliters.

(ii) For sterility testing; 10 approximately equal portions of at least 1 milliliter.

Each such portion shall be taken from different parts of such batch, and each shall be packaged in a separate container and in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) and (iii) of this paragraph, and no sample referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) (*a*) and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (4) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.68 Benzathine penicillin G (benzathine penicillin G salt).

(a) *Standards of identity, strength, quality, and purity.* Benzathine penicillin G is the crystalline N,N'dibenzylethylenediamine salt of penicillin G. It contains not less than 85 percent by weight of the N,N'dibenzylethylenediamine salt of penicillin G. Each such drug is so purified and dried that:

(1) Its potency is not less than 1050 units per milligram.

(2) It is sterile.

(3) It is nontoxic.

(4) It is nonpyrogenic.

(5) Its moisture content is not more than 8 percent.

(6) Its pH in a saturated aqueous solution is not less than 5.0 and not more than 7.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The weight of the drug and the number of units in the immediate container.

(3) The statement "Expiration date ----------," the blank being filled in with the date which is 36 months after the month during which the batch was certified.

(4) The statement "For manufacturing use only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH crystallinity, and the penicillin G content.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which benzathine penicillin G is to be used, the manufacturer of a batch which is to be so used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10 for all containers submitted in accordance with paragraph (d) (2) (ii) of this section.

(2) If the Commissioner considers that investigations, other than the examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.69 Benzathine penicillin G oral suspension, benzathine penicillin G for oral suspension (benzathine penicillin G powder).

(a) *Standards of identity, strength, quality, and purity.* Benzathine penicillin G oral suspension is an aqueous suspension of benzathine penicillin G, and benzathine penicillin G for oral suspension is a dry mixture of benzathine penicillin G; each drug may contain one or more suitable and harmless dispersing agents, buffer substances, and preservatives, with or without one or more suitable sulfonamides and suitable and harmless colorings and flavorings. Unless it is intended solely for veterinary use, the potency of the oral suspension and of the suspension prepared as directed in its labeling is not less than 20,000 units per milliliter. Its pH is not less than 6.0 and not more than 7.0. If it is a dry mixture of the drug, its moisture content is not more than 6.0 percent. The benzathine penicillin G used conforms to the requirements of § 146a.68 (a), except subparagraphs (2), (4), and, if it is the oral suspension, (5) of that paragraph. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the requirements prescribed by § 1.106(b) of this chapter

(regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that if it is the dry mixture of the drug the blank may be filled in with the date that is 36 months after the month during which the batch was certified, if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him conforms with the standards prescribed by paragraph (a) of this section.

(ii) On the label and labeling, if sulfonamides are present, after the name "benzathine penicillin G oral suspension" or "benzathine penicillin G for oral suspension," wherever it appears, the words "with sulfonamides," in juxtaposition with such name.

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all of the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the benzathine penicillin G used in making such batch was completed, the potency per milliliter if it is a suspension of the drug and the number of units in each immediate container if it is a dry mixture, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per milliliter if it is the oral suspension, average potency per immediate container if it is a dry mixture, pH, and moisture if it is a dry mixture of the drug.

(ii) The benzathine penicillin G used in making the batch; potency, toxicity, pH, moisture (if it is used in the preparation of a dry mixture), crystallinity, and the penicillin G content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The benzathine penicillin G used in making the batch; 10 packages, each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146a.68 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than the examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of benzathine penicillin G oral suspension and benzathine penicillin G for oral suspension for veterinary use from certification.* Benzathine penicillin G oral suspension and benzathine penicillin G for oral suspension that conform to the requirements of paragraphs (a) (except that they may contain one or more essential vitamins and mineral substances for nutritive purposes), (b), and (c) of this section shall be exempt from the requirements of sections 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) They are intended solely for veterinary use and are conspicuously so labeled.

(2) If they contain added vitamins or minerals, the labels bear the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear an expiration date that is not more than 24 months after the month during which the batch was last assayed and released by the manufacturer.

(4) The labels bear a statement that solutions prepared with the drugs are stable for not more than 24 hours.

(5) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Chronic respiratory disease (air-sac infection) in chickens.

(ii) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(iii) Infectious sinusitis in poultry.

§ 146a.70 Penicillin-streptomycin bacitracin ointment; penicillin-dihydrostreptomycin-bacitracin ointment; penicillin - streptomycin - bacitracin methylene disalicylate ointment; penicillin-dihydrostreptomycin-bacitracin methylene disalicylate ointment.

(a) Penicillin-streptomycin-bacitracin ointment, penicillin-dihydrostreptomycin-bacitracin ointment, penicillin-streptomycin-bacitracin methylene disalicylate ointment, and penicillin-dihydrostreptomycin-bacitracin methylene disalicylate ointment conform to all requirements prescribed by § 146a.54 for penicillin-streptomycin ointment and penicillin - dihydrostreptomycin ointment, except that:

(1) It contains the equivalent of not less than 500 units of bacitracin per gram, except if it is intended for udder instillation in cattle each dose, as recommended in its labeling, shall contain not less than the equivalent of 5,000 units of bacitracin. The bacitracin used conforms to the standards prescribed therefor by § 146e.401(a) of this chapter except paragraph (a) (2), (3), (4), and (8) of that section. The bacitracin methylene disalicylate used conforms to the requirements of § 146e.416 (a) of this chapter.

(2) [Reserved]

(3) In addition to complying with requirements of § 146a.54 (c), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the bacitracin or bacitracin methylene disalicylate used in making the batch for potency, moisture, pH, and ash content. He shall also submit in connection with his request a sample consisting of not less than 7 packages of such ointment and (unless it was previously submitted) a sample consisting of 6 packages containing approximately equal portions of not less than 0.5 gram each of the bacitracin or bacitracin methylene disalicylate used in making the batch, packaged in accordance with the requirements of § 146e.401 (b) of this chapter.

(b) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (a) (3) of this section shall be:

(1) $6.00 for each immediate container of ointment submitted.

(2) $4.00 for each immediate container of bacitracin or bacitracin methylene disalicylate submitted.

§ 146a.71 Penicillin-streptomycin dental cones; penicillin-dihydrostreptomycin dental cones.

(a) Penicillin-streptomycin dental cones and penicillin-dihydrostreptomy-

cin dental cones conform to all requirements prescribed by § 146a.31 for penicillin dental cones and are subject to all procedures prescribed by that section for penicillin dental cones, except that:

(1) Each cone contains not less than 25 milligrams of streptomycin or dihydrostreptomycin. The streptomycin used conforms to the standards prescribed by § 146b.101 (a) of this chapter, except subparagraphs (2), (4), and (5) of that paragraph. The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103 of this chapter, except the standards for sterility, pyrogens, and histamine.

(2) Its moisture content is not more than 3 percent.

(3) An expiration date of 48 months or 60 months after the month during which the batch was certified may be used if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him conforms with the standards prescribed in subparagraphs (1) and (2) of this paragraph.

(4) In addition to complying with the requirements of § 146a.31 (d), the person who requests certification of a batch of penicillin-streptomycin dental cones or penicillin-dihydrostreptomycin dental cones shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin and crystallinity if it is crystalline dihydrostreptomycin, and the number of units of penicillin and the number of milligrams of streptomycin or dihydrostreptomycin in each cone of the batch. He shall also submit in connection with his request (unless previously submitted) a sample consisting of 6 packages containing approximately equal portions of not less than 0.5 gram each of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101b of this chapter.

(b) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (a) (4) of this section shall be:

(1) $1.00 for each cone submitted in accordance with the requirements of § 146a.31 (d) (3) (i) (*a*) and (*c*).

(2) $4.00 for each immediate container in the sample of streptomycin or dihydrostreptomycin submitted.

§ 146a.72 Hydrabamine penicillin V (penicillin V hydrabamine salt).

(a) *Standards of identity, strength, quality, and purity.* Hydrabamine penicillin V is the crystalline hydrabamine salt of penicillin V. It contains not less than 90 percent of the hydrabamine salt of penicillin V. It is so purified and dried that:

(1) Its potency is not less than 825 units per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 2 percent.

(4) Its pH in a saturated aqueous solution is not less than 3.0 and not more than 6.5.

(5) Its extinction coefficient $E^{1\%}_{1\ cm.}$ is not less than 8.0 at 276 mμ.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of units per milligram and the number of grams in the immediate container.

(3) The statement "Expiration date ---------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(4) The statement "For use in the manufacture of nonparenteral drugs only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, crystallinity, the penicillin V content, and extinction coefficient.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of 10 packages, each containing approximately 300 milligrams taken from a different part of such batch, packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.73 Hydrabamine penicillin V oral suspension.

Hydrabamine penicillin V oral suspension conforms to all requirements and is subject to all procedures prescribed by § 146a.98 for hydrabamine penicillin G oral suspension, except that:

(a) Hydrabamine penicillin V is used in lieu of hydrabamine penicillin G. The hydrabamine penicillin V used conforms to the requirements of § 146a.72 (a).

(b) Its pH is not less than 4.5 and not more than 6.5.

(c) In lieu of the directions prescribed by § 146a.98 (d) (2) (ii), a person who requests certification of a batch shall submit in connection with his request results of the tests and assays made by him on an accurately representative sample of the hydrabamine penicillin V used in making the batch for potency, toxicity, moisture, pH, crystallinity, the penicillin V content, and the extinction coefficient.

§ 146a.74 Diethylaminoethyl ester penicillin G hydriodide (penicillin G diethylaminoethyl ester hydriodide).

(a) *Standards of identity, strength, quality, and purity.* Diethylaminoethyl ester penicillin G hydriodide is the crystalline diethylaminoethyl ester hydriodide salt of penicillin G. It contains not less than 85 percent by weight of β-diethylaminoethyl ester hydriodide salt of penicillin G. It is so purified and dried that:

(1) Its potency after hydrolysis is not less than 900 units per milligram.

(2) It is sterile.

(3) It is nonpyrogenic.

(4) It is nontoxic.

(5) Its moisture content is not more than 1 percent.

(6) The pH of a saturated aqueous solution is not less than 4.0 and not more than 6.5.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear, on its outside wrapper or container and the immediate container as hereinafter indicated, the following:

(1) The batch mark.

(2) The weight of the drug and the number of units in the immediate container.

(3) The statement "Expiration date ----------," the blank being filled in with the date which is 24 months after the month during which the batch was certified.

(4) The statement "For manufacturing use only."

(5) The statement 'Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addi-

tion to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him for potency, sterility, toxicity, pyrogens, moisture, pH, crystallinity, and the penicillin G content.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which it is to be used, the manufacturer of a batch which is to be so used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drugs. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.75 Diethylaminoethyl ester penicillin G hydriodide for aqueous injection (penicillin G diethylaminoethyl ester hydriodide for aqueous injection).

(a) *Standards of identity, strength, quality, and purity.* Diethylaminoethyl ester penicillin G hydriodide for aqueous injection is diethylaminoethyl ester penicillin G hydriodide and one or more suitable and harmless suspending or dispersing agents, with or without one or more suitable and harmless preservatives and buffer substances. It is so purified and dried that:

(1) It is sterile.

(2) Its moisture content is not more than 1 percent.

(3) It is nonpyrogenic.

(4) It is nontoxic.

(5) The pH of a saturated aqueous solution is not less than 5.0 and not more than 7.5.

The diethylaminoethyl ester penicillin G hydriodide used conforms to the requirements of § 146a.74 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container shall contain 500,000 units or multiples thereof up to and including 5,000,000 units, and each may be packaged in combination with a container of a suitable aqueous diluent.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date ---------," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) On the circular or other labeling within or attached to the package, the conditions under which suspensions of the drug may be stored, and the statement "Sterile suspension may be kept at room temperature for 7 days, or in refrigerator for 3 weeks, without significant loss of potency."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the diethylaminoethyl ester penicillin G hydriodide used in making such batch was completed, the number of units in each such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section. If such batch, or any part thereof, is to be packaged with a solvent, such request shall be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture, pyrogens, toxicity, pH.

(ii) The diethylaminoethyl ester penicillin G hydriodide used in making the batch; potency, crystallinity, penicillin G content.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(a) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(b) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The diethylaminoethyl ester penicillin G hydriodide used in making the batch; 3 packages containing approximately equal portions of not less than 500 milligrams each, packaged in accordance with the requirements of § 146a.74 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(iv) In the case of an initial request for the certification of a batch which is to be packaged in combination with an aqueous diluent which is not recognized by the U. S. P., or when any change is made in the composition of such diluent; 5 packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility: 10 packages.

(ii) For sterility testing: 10 packages.

Each such package shall contain approximately 300 milligrams, taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), (iii), (iv), and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (4) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.76 Penicillin-streptomycin implantation pellets; penillicin-dihydrostreptomycin implantation pellets.

(a) *Standards of identity, strength, quality, and purity.* Penicillin-streptomycin implantation pellets and penicillin-dihydrostreptomycin implantation pellets are pellets composed of crystalline penicillin or procaine penicillin and streptomycin or dihydrostreptomycin, with or without the addition of one or more suitable and harmless diluents, binders, and lubricants. Each pellet contains not less than 5,000 units of penicillin and not less than 6.25 milligrams of streptomycin or dihydrostreptomycin. Its moisture content is not more than 5 percent. The crystalline penicillin conforms to the requirements of § 146a.24 (a), except subparagraphs (2) and (4) of that paragraph. The procaine penicillin conforms to the requirements of § 146a.44(a), except subparagraphs (2) and (3) of that paragraph. The streptomycin used conforms to the requirements of § 146.101(a) of this chapter, except § 146b.101(a) (2), (4), and (5). The dihydrostreptomycin used conforms to the requirements of § 146b.103 of this chapter, except the standards for sterility, pyrogens, and histamine content. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the requirements prescribed therefor by such official compendium.

(b) *Packaging.* Unless each pellet is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the pellets by a plug of cotton or other like material. The composition of the immediate container or of the foil or film enclosure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of units of penicillin in each pellet of the batch.

(iii) The number of milligrams of streptomycin or dihydrostreptomycin in each pellet of the batch.

(iv) The statement "For veterinary use only."

(v) The statement "Expiration date _____," the blank being filled in with the date which is 18 months after the month during which the batch was certified.

(2) On the circular or other labeling within or attached to the package, if it is packaged for dispensing, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of pellets in such batch, the number of pellets of the batch packaged into dispensing-size containers during each day's packaging operations, the number of units of penicillin and the number of milligrams of streptomycin or dihydrostreptomycin in each pellet, the date on which the latest assay of the drug comprising such batch was completed, the date (unless submitted previously) on which the latest assay of the penicillin and streptomycin or dihydrostreptomycin, used in making the batch was completed, the quantity of each ingredient used in making the batch, and a statement that such ingredient conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: Average potency and average moisture of pellets collected during the time of making the batch, and, unless the pellets are packaged into dispensing-size containers immediately after they are compressed, average moisture of pellets collected during each day of packaging the batch.

(*b*) If the person who requests certification is not the manufacturer of the batch: Average potency and average moisture of pellets collected during each day the pellets are being packaged into dispensing-size containers.

(ii) The penicillin used in making the batch; potency, toxicity, moisture, pH, crystallinity, and heat stability (unless it is procaine penicillin), penicillin K content (unless it is crystalline penicillin G or procaine penicillin G), and the penicillin G content if it is crystalline penicillin G or procaine penicillin G.

(iii) The streptomycin or dihydrostreptomycin used in making the batch; potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If the person who requests certification is the manufacturer of the batch: One pellet for each 5,000 pellets in the batch, but in no case less than 30 pellets collected by taking single pellets throughout the entire time of making the batch that the quantities made during the intervals are approximately equal.

(*b*) If, after making, such person packages the batch into dispensing-size containers: 20 pellets collected at equal intervals during each day the pellets are being packaged, except that this sample is not required if the pellets are packaged immediately after they are made; or

(*c*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of pellets filled by such person into dispensing-size containers during each day's packaging operations): One pellet for each 5,000 pellets in the batch, but in no case less than 30 pellets collected, by taking single pellets at such intervals throughout each day of packaging the pellets that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is crystalline penicillin and not less than 300 milligrams if it is procaine penicillin, each taken from a different part of such batch and packaged in accordance with the requirements of § 146a.24 (b) or § 146a.44 (b).

(iii) The streptomycin or dihydrostreptomycin used in making the batch; 5 packages, each containing approximately 0.5 gram, taken from a different part of such batch and packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(iv) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) and (iii) of this paragraph, and no sample referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $1.00 for each pellet in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) and (*c*) of this section; $3.00 for the sample submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section.

(2) If the Commissioner considers that investigations other than examination of such pellets and packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.77 Benzathine penicillin G for aqueous injection.

(a) *Standards of identity, strength, quality, and purity.* Benzathine penicillin G for aqueous injection is a dry mixture of benzathine penicillin G and one or more suitable and harmless suspending or dispersing agents and with or without one or more suitable and harmless preservatives, buffer substances, and local anesthetics; or it is an aqueous suspension of benzathine penicillin G and one or more suitable and harmless suspending or dispersing agents, buffer substances, and preservatives and with or without one or more suitable and harmless local anesthetics. It is so purified that:

(1) If it is an aqueous suspension of the drug, each container or each milliliter shall contain not less than 300,000 units.

(2) It is sterile.

(3) If it is the dry mixture of the drug, its moisture content is not more than 8 percent.

(4) It is nonpyrogenic.

(5) It is nontoxic.

(6) Its pH in saturated solution is not less than 5.0 and not more than 7.5.

The benzathine penicillin G used conforms to the requirements of § 146a.68 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless, (unless it is intended solely for veterinary use) transparent glass, closed by a substance through which a hyprodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. If it is the dry mixture of the drug, each such container shall contain 300,000 units, 600,000 units, 900,000 units, 1,200,000 units, 1,500,000 units, 2,400,000 units, or 3,000,000 units, unless it is intended solely for veterinary use and is conspicuously so labeled. Each such container may be packaged in combination with a container of a suitable aqueous diluent. If it is the aqueous suspension of the drug, each such container shall contain not less than 1 milliliter (unless it is packaged to contain a single dose) and not more than 10 milliliters (unless it is intended solely for veterinary use and is conspicuously so labeled), and each shall be filled with a volume in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated, whether administered in either single or multiple doses.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the requirements of § 1.106 (b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label and labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement "Expiration date ----------," the blank being filled in, if it is a dry mixture of the drug, with the date that is 48 months, or if it is the aqueous suspension of the drug, with the date that is 18 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified, if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(*b*) If it is the aqueous suspension of the drug, the statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)," unless the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section after having been stored at room temperature.

(ii) On the circular or other labeling within or attached to the package, if it is the dry mixture of the drug, the conditions under which suspensions made from such drug should be stored, and the statement "Sterile suspension may be kept at room temperature for 1 week, or in refrigerator for 3 weeks, without significant loss of potency."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of benzathine penicillin G for aqueous injection shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the benzathine penicillin G used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section. If such batch, or any part thereof, is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: potency, sterility, moisture (unless it is an aqueous suspension of the drug), pyrogens, toxicity, pH.

(ii) The benzathine penicillin G used in making the batch; potency, penicillin G content, crystallinity.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The benzathine penicillin G used in making the batch; three packages containing approximately equal portions of not less than 500 milligrams each, packaged in accordance with the requirements of § 146a.68 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch of benzathine penicillin G for aqueous injection which is to be packaged in combination with an aqueous diluent which is not recognized by the U. S. P., or when any change is made in the composition of such diluent, five packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain not less than approximately 300 milligrams taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), (iii), (iv), and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (4) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.78 Benzathine penicillin G and buffered crystalline penicillin for aqueous injection.

(a) Benzathine penicillin G and buffered crystalline penicillin for aqueous injection conforms to all requirements prescribed by § 146a.77 for the dry mixture of penicillin G for aqueous injection, and is subject to all procedures prescribed by § 146a.77 for the dry mixture of benzathine penicillin G for aqueous injection, except that:

(1) Each immediate container shall contain not less than 50,000 units of buffered crystalline penicillin for each 300,000 units of benzathine penicillin G. The buffered crystalline penicillin conforms to the requirements prescribed therefor by § 146a.37.

(2) The circular or other labeling within or attached to the package shall bear in lieu of the statement prescribed by § 146a.77(c) (1) (ii), the statement "Sterile suspension may be kept in refrigerator for 1 week without significant loss of potency."

(3) In addition to complying with the requirements of § 146a.77 (d), a person who requests certification of a batch of benzathine penicillin G and buffered crystalline penicillin for aqueous injection shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and date of the latest tests and assays of the buffered crystalline penicillin used in making the batch for potency, crystallinity, heat stability, penicillin K content (unless it is buffered crystalline penicillin G) and the penicillin G content if it is buffered crystalline penicillin G, the number of units of benzathine penicillin G and the number of units of buffered crystalline penicillin in each immediate container of the batch. He shall also submit in connection with his request a sample consisting of three packages containing approximately equal portions of not less than 250 milligrams each of the buffered crystalline penicillin used in making the batch. If such batch is packaged for repacking, each portion in the sample required by § 146a.77 (d) (4) shall consist of approximately 400 milligrams in lieu of 300 milligrams.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (3) of this section shall be:

(1) $5.00 for each immediate container of the sample submitted in accordance with § 146a.77 (d) (4).

(2) $4.00 for each immediate container of buffered crystalline penicillin submitted.

§ 146a.79 Chloroprocaine penicillin O (penicillin O chloroprocaine salt).

(a) *Standards of identity, strength, quality, and purity.* Chloroprocaine penicillin O is the crystalline 2-chloroprocaine salt of penicillin O prepared from 2-chloroprocaine hydrochloride (95 percent purity and a melting point of 171°–176° C.) and crystalline penicillin O. It contains not less than 85 percent of the 2-chloroprocaine salt of penicillin O and not more than 0.5 percent of the 2-chloroprocaine salt of penicillin G. Each such drug is so purified and dried that:

(1) Its potency is not less than 850 units per milligram.

(2) It is sterile.

(3) It is nonpyrogenic.

(4) It is nontoxic.

(5) Its moisture content is not more than 4.2 percent.

(6) Its pH in saturated aqueous solution is not less than 5.0 and not more than 7.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of chloroprocaine penicillin O shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The weight of the drug and the number of units in the immediate container.

(3) The statement "Expiration date ----------," the blank being filled in with the date which is 36 months after the month during which the batch was certified.

(4) The statement "For manufacturing use only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chloroprocaine penicillin O shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH, crystallinity, chloroprocaine penicillin O content, and chloroprocaine penicillin G content.

(2) Such person shall submit in connection with his request an accurately representative sample of the batch:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 300 milligrams taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which chloroprocaine penicillin O is to be used, the manufacturer of a batch which is so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (2) of this

paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (i) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.80 Chloroprocaine penicillin O for aqueous injection.

(a) *Standards of identity, strength, quality, and purity.* Chloroprocaine penicillin O for aqueous injection is a dry mixture of chloroprocaine penicillin O and one or more suitable and harmless suspending or dispersing agents, with or without one or more suitable and harmless buffer substances. It is so purified and dried that:

(1) It is sterile.

(2) Its moisture content is not more than 4.2 percent.

(3) It is nonpyrogenic.

(4) It is nontoxic.

(5) Its pH in saturated aqueous solution is not less than 5.0 and not more than 7.5.

The chloroprocaine penicillin O used conforms to the requirements of § 146a.79 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless, transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container shall contain 300,000 units, 600,000 units, 900,000 units, 1,200,000 units, 1,500,000 units, or 3,000,000 units, unless it is intended solely for veterinary use and is conspicuously so labeled. Each such container may be packaged in combination with a container of a suitable aqueous diluent.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the requirements of § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label and labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 36 months after the month during which the batch was certified.

(ii) On the circular or other labeling within or attached to the package, the conditions under which suspensions made from such drug should be stored, and the statement "Sterile suspension may be kept at room temperature for 1 week, or in refrigerator for 3 weeks, without significant loss of potency."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chloroprocaine penicillin O for aqueous injection shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chloroprocaine penicillin O used in making such batch was completed, the number of units in each of such packages, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section. If such batch, or any part thereof, is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture, pyrogens, toxicity, pH.

(ii) The chloroprocaine penicillin O used in making the batch; potency crystallinity, penicillin O content, and penicillin G content.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chloroprocaine penicillin O used in making the batch: six packages containing approximately equal portions of not less than 300 milligrams each.

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5.0 grams.

(iv) In case of an initial request for the certification of a batch of chloroprocaine penicillin O for aqueous injection which is to be packaged in combination with an aqueous diluent which is not recognized by the U. S. P., or when any change is made in the composition of such diluent, five packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain not less than approximately 300 milligrams taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraphs (d) (3) (i) (*a*), (ii), (iii), and (iv) and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (4) (ii) of this section."

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the

request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.81 Penicillin-streptomycin vaginal suppositories; penicillin-dihydrostreptomycin vaginal suppositories.

(a) Penicillin - streptomycin vaginal suppositories and penicillin-dihydrostreptomycin vaginal suppositories conform to all requirements prescribed by § 146a.36 for penicillin vaginal suppositories and are subject to all procedures prescribed by that section for penicillin vaginal suppositories, except that:

(1) Each suppository shall contain not less than 200 milligrams of streptomycin or dihydrostreptomycin. The streptomycin used conforms to the standards prescribed by § 146b.101 (a) of this chapter, except § 146b.101 (a) (2), (3), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103 of this chapter, except the standards for sterility, toxicity, pyrogens, and histamine.

(2) [Reserved]

(3) In addition to complying with the requirements of § 146a.36 (d), a person who requests certification of a batch of penicillin-streptomycin vaginal suppositories or penicillin-dihydrostreptomycin vaginal suppositories shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, moisture, pH, streptomycin content if it is dihydrostreptomycin and crystallinity if it is crystalline dihydrostreptomycin, and the number of units of penicillin and the number of milligrams of streptomycin or dihydrostreptomycin in each suppository in the batch. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 6 packages containing approximately equal portions of not less than 0.5 gram each of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101(b) of this chapter.

(b) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (a) (3) of this section shall be:

(1) $1.00 for each suppository submitted in accordance with the requirements of § 146a.36(d) (3) (i) (*a*) and (*c*).

(2) $4.00 for each immediate container of streptomycin or dihydrostreptomycin submitted.

§ 146a.82 Penicillin-streptomycin-bacitracin dental paste; penicillin-dihydrostreptomycin-bacitracin dental paste.

(a) *Standards of identity, strength, quality, and purity.* Penicillin-streptomycin-bacitracin dental paste and penicillin - dihydrostreptomycin - bacitracin dental paste is calcium penicillin, crystalline sodium or potassium penicillin, or procaine penicillin, streptomycin or dihydrostreptomycin, bacitracin, and sodium caprylate in a suitable and harmless base. Its moisture content is not more than 2 percent. It contains not less than 200,000 units of penicillin, not less than 2,000 units of bacitracin, and not less than 0.20 gram of streptomycin or dihydrostreptomycin per milliliter. The calcium penicillin or crystalline penicillin used conforms to the requirements of § 146a.24 (a) except the limitation on penicillin K content, and except subparagraphs (1) and (4) of that paragraph, but its potency is not less than 300 units per milligram. The procaine penicillin used conforms to the requirements of § 146a.44 (a) except subparagraph (3) of that paragraph. The streptomycin used conforms to the standards prescribed by § 146b.101 (a) of this chapter except subparagraphs (4) and (5) of that paragraph. The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103 of this chapter except the standards for pyrogens and histamine. The bacitracin used conforms to the standards prescribed therefor by § 146e.401 (a) of this chapter except § 146e.401(a) (4) and (8).

(b) *Packaging.* The drug shall be packaged in immediate containers of transparent glass which meet the test for tight containers as defined by the U. S. P. Each such glass container shall be so sealed that the contents cannot be used without destroying such seal and shall be closed by a substance through which a hypodermic needle may be introduced and withdrawn without destroying its effectiveness. The immediate container and closure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106 (b) of this chapter (regulations issued under section 502(f) of the act), each package of the drug shall bear on the outside wrapper or container and the immediate container the following:

(1) The statement, "For endodontic use only."

(2) The statement, "Expiration date ----------," the blank being filled in with the date that is not more than 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(3) On the circular or other labeling within or attached to the package, if it is packaged for dispensing, adequate directions and warnings for its use by practitioners licensed by law to administer such drug.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of penicillin-streptomycin-bacitracin dental paste or penicillin-dihydrostreptomycin-bacitracin dental paste shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark, and (unless they were previously submitted) the dates of the latest tests and assays of the penicillin, streptomycin or dihydrostreptomycin, and bacitracin used in making the batch.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, and moisture.

(ii) The penicillin used in making the batch; potency, toxicity, sterility, moisture, pH, crystallinity if it is crystalline penicillin, heat stability if it is crystalline sodium or potassium penicillin, the penicilln G content if it is crystalline sodium or potassium penicillin G, and the procaine penicillin G content if it is procaine penicillin G.

(iii) The streptomycin or dihydrostreptomycin used in making the batch; potency, toxicity, sterility, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(iv) The bacitracin used in making the batch; potency, toxicity, sterility, moisture, pH, and ash content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one package for each 5,000 packages in the batch, but in no case less than 7 packages.

(*b*) For sterility testing; 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch:

(*a*) For all tests except sterility; 5 packages, or in the case of crystalline penicillin, 10 packages, each containing approximately equal portions of not less than 60 milligrams if it is not procaine penicillin, and not less than 300 milligrams if it is procaine penicillin.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of 300 milligrams.

Such samples shall be packaged in accordance with the requirements of § 146a.24 (b) or § 146a.44 (b).

(iii) The streptomycin or dihydrostreptomycin used in making the batch:

(*a*) For all tests except sterility; 5 packages containing approximately equal portions of not less than 0.5 gram.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of 0.5 gram.

Such samples shall be packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(iv) The bacitracin used in making the batch:

(*a*) For all tests except sterility; 6 packages, each containing approximately equal portions of not less than 0.5 gram.

(*b*) For sterility testing; 10 packages, each containing approximately equal portions of 0.5 gram.

Such samples shall be packaged in accordance with the requirements of § 146e.401 (b) of this chapter.

(v) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii), (iii), and (iv) of this paragraph, and no sample referred to in subparagraph (3) (ii), (iii), and (iv) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of penicillin-streptomycin-bacitracin dental paste or penicillin-dihydrostreptomycin-bacitracin dental paste under the regulations in this part shall be:

(1) $4.00 for each immediate container submitted in accordance with paragraph (d) (3) (ii) (*a*), (iii) (*a*), (iv) (*a*), and (v) of this section; $6.00 for each immediate container submitted in accordance with paragraph (d (3) (i) (*a*) of this section; $4.00 for each immediate container submitted in accordance with paragraph (d) (3) (ii) (*a*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*), (ii) (*b*), (iii) (*b*), and (iv) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.83 Procaine penicillin-streptomycin-neomycin-erythromycin in oil; procaine penicillin-dihydrostreptomycin-neomycin-erythromycin in oil.

Procaine penicillin-streptomycin-neomycin-erythromycin in oil and procaine penicillin-dihydrostreptomycin - neomycin-erythromycin in oil conform to all requirements and are subject to all procedures prescribed by § 146a.89 for procaine penicillin-streptomycin-neomycin in oil and procaine penicillin-dihydrostreptomycin-neomycin in oil, except that:

(a) (1) It contains not less than 5.0 milligrams of erythromycin per milliliter, except if it is intended solely for use in the eyes and ears of veterinary animals and it is conspicuously so labeled it may contain not less than 3.5 milligrams per milliliter. The erythromycin used conforms to the standards prescribed by § 146b.121(a) of this chapter.

(2) If it is intended solely for use in the eyes and ears of veterinary animals and is conspicuously so labeled, it may contain chlorhexidine dihydrochloride (bis-(*p*-chlorophenyl diguanido)-hexane dihydrochloride).

(b) Each package shall also bear on its label and labeling, if it contains the active ingredient specified in paragraph (a)(2) of this section, after the name "procaine penicillin - streptomycin - neomycin-erythromycin in oil" or "procaine penicillin - dihydrostreptomycin - erythromycin in oil," wherever it appears, the words "with ---------- (the blank being filled in with the words 'chlorhexidine dihydrochloride')," in juxtaposition with such name.

(c) In addition to complying with the requirements of § 146a.89 (c), a person who requests certification of a batch shall submit with his request a statement showing the number of milligrams of erythromycin in each milliliter of the batch, the batch mark, and (unless they were previously submitted) the results and the date of the latest tests and assays of the erythromycin used in making the batch for potency, moisture, pH, and color-identity test. He shall also submit in connection with his request a sample consisting of not less than eight immediate containers of the batch and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the erythromycin used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (c) of this section shall be:

(1) $6.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of the erythromycin used in making the batch.

§ 146a.84 Penicillin and dihydrostreptomycin-streptomycin sulfates veterinary; procaine penicillin in dihydrostreptomycin-streptomycin sulfates solution veterinary.

(a) *Standards of identity, strength, quality, and purity.* Penicillin and dihydrostreptomycin-streptomycin sulfates veterinary and procaine penicillin in dihydrostreptomycin-streptomycin sulfates solution veterinary conform to the standards prescribed by § 146b.113(a) of this chapter for dihydrostreptomycin-streptomycin sulfates veterinary, except that:

(1) It contains dry procaine penicillin, benzathine penicillin G, crystalline penicillin O, chloroprocaine penicillin O, crystalline sodium penicillin or potassium penicillin, or a mixture of any combination of such salts, or it contains procaine penicillin suspended in an aqueous solution of dihydrostreptomycin-streptomycin sulfates. The procaine penicillin used conforms to the requirements prescribed by § 146a.44 (a). The crystalline penicillin used conforms to the requirements prescribed for crystalline penicillin by § 146a.24 (a). The benzathine penicillin G used conforms to the requirement prescribed by § 146a.68 (a). The crystalline penicillin O used conforms to the requirements prescribed by § 146a.24 (a). The chloroprocaine penicillin O used conforms to the requirements prescribed by § 146a.79 (a).

(2) It may contain suitable and harmless buffer substances, preservatives, suspending, dispersing, and stabilizing agents. Each such substance, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(3) The moisture content of the dry mixture is not more than 3.5 percent, except if it contains procaine penicillin or chloroprocaine penicillin O, its moisture content is not more than 4.2 percent, and if it contains benzathine penicillin G its moisture content is not more than 6 percent.

(4) The pH of a solution or a suspension prepared as directed in its labeling is not less than 5.0 and not more than 7.5.

(b) *Packaging.* It shall be packaged in accordance with the requirements prescribed by § 146b.113 (b) of this chapter, except that each immediate container or each milliliter shall contain not less than 300,000 units of penicillin, 0.125 gram dihydrostreptomycin, and 0.125 gram streptomycin.

(c) *Labeling.* If it is a dry mixture it shall be labeled in accordance with the requirements prescribed by § 146a.58(c). If it is a suspension of the drug, it shall be labeled in accordance with the requirements prescribed by § 146a.67(c).

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146b.113 (d) (1) of this chapter, a person who requests certification of a batch shall submit a statement showing the dates on which the latest assays of the penicillin used in making the batch were completed (unless they were previously submitted), the batch marks, and the content of each salt of penicillin in each container.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request, results of the tests and assays listed after each of the following made by him on an accurately representative sample of:

(i) The batch; content of each salt of penicillin, content of dihydrostreptomycin and streptomycin, sterility, toxicity, pyrogens, moisture (if it is the dry mixture), and pH.

(ii) The procaine penicillin used in making the batch; potency, crystallinity, penicillin K content (unless it is penicillin G) and the penicillin G content if it is procaine penicillin G.

(iii) The crystalline sodium or potassium penicillin used in making the batch; potency, crystallinity, heat stability, penicillin K content (unless it is crystalline penicillin G), and the penicillin G content if it is crystalline penicillin G.

(iv) The benzathine penicillin G used in making the batch; potency, crystallinity, and penicillin G content.

(v) The crystalline penicillin O used in making the batch; potency, crystallinity, heat stability, penicillin O content, and penicillin G content.

(vi) The chloroprocaine penicillin O used in making the batch; potency, crystallinity, chloroprocaine penicillin O content, and chloroprocaine penicillin G content.

(vii) The dihydrostreptomycin and streptomycin used in making the batch; potency, histamine content, and crystallinity if it is crystalline dihydrostreptomycin.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 13 (14, if it contains benzathine penicillin G) or more than 19 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The procaine penicillin used in making the batch; 3 packages containing approximately equal portions of not less than 0.5 gram, each packaged in accordance with the requirements of § 146a.44 (b).

(iii) The crystalline penicillin used in making the batch; 3 packages containing approximately equal portions of not less than 250 milligrams, each packaged in accordance with the requirements of § 146a.24 (b).

(iv) The benzathine penicillin G used in making the batch; 3 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146a.68 (b).

(v) The crystalline penicillin O and the chloroprocaine penicillin O used in making the batch; 3 packages of each, containing approximately equal portions of not less than 300 milligrams each, packaged in accordance with the requirements of § 146a.24 (b) and § 146a.79 (b).

(vi) The dihydrostreptomycin and streptomycin used in making the batch; 6 packages of each salt containing approximately equal portions of not less than 0.5 gram, each packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(vii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5.0 grams.

(4) If such batch is packaged for repacking such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility; 13 (14, if it contains benzathine penicillin G) approximately equal portions of at least 2.0 grams.

(ii) For sterility testing; 10 approximately equal portions of at least 0.5 gram.

Each such portion shall be taken from a different part of such batch and each shall be packaged in a separate container and in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii), (iii), (iv), (v), (vi), and (vii) of this paragraph, and no sample referred to in subparagraph (3) (ii), (iii), (iv), (v), and (vi) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), (v), (vi), and (vii) of this section; $6.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) (*a*) and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (4) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigation.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.85 Benzathine-procaine-buffered crystalline penicillins for aqueous injection.

Benzathine-procaine-buffered crystalline penicillins for aqueous injection conforms to all requirements prescribed by § 146a.50 for procaine penicillin and buffered crystalline penicillin for aqueous injection, except paragraph (b) of that section and is subject to all procedures prescribed by § 146a.50 for procaine penicillin and buffered crystalline penicillin for aqueous injection, except that:

(a) Each immediate container shall contain not less than 200,000 units of benzathine penicillin G, 200,000 units of procaine penicillin, and 100,000 units of buffered crystalline penicillin. The benzathine penicillin G used conforms to the requirements prescribed therefor by § 146a.68.

(b) Its moisture content is not more than 6 percent.

(c) In addition to complying with the requirements of § 146a.50(d), a person who requests certification of a batch of benzathine procaine-buffered crystalline penicillins for aqueous injection shall submit with his request a statement showing the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the benzathine penicillin G used in making the batch for potency, crystallinity, and penicillin G content, and the number of units of benzathine penicillin G in each container of the batch. He shall also submit in connection with his request a sample consisting of three packages containing approximately equal portions of not less than 0.5 gram each of the benzathine penicillin G used in making the batch. If such batch is packaged for repacking, each portion in the sample required by § 146a.50(d) shall consist of approximately 0.5 gram in lieu of 400 milligrams.

(d) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (c) of this section shall be:

(1) $6.00 for each immediate container of the batch submitted in accordance with § 146a.47(d) (3) (i) (*a*) and (4) (i).

(2) $4.00 for each immediate container of benzathine penicillin G submitted in accordance with paragraph (c) of this section.

§ 146a.86 Benzathine penicillin G and procaine penicillin for aqueous injection.

Benzathine penicillin G and procaine penicillin for aqueous injection conforms to all requirements, and is subject to all procedures, prescribed by § 146a.77 for benzathine penicillin G for aqueous injection, except that:

(a) Each container shall contain not less than 300,000 units of benzathine penicillin G and not less than 300,000 units of procaine penicillin. The procaine penicillin used conforms to the requirements prescribed therefor by § 146a.44 (a).

(b) If it is the dry mixture of the drug, its moisture content is not more than 6.0 percent.

(c) In lieu of the directions for labeling prescribed by § 146a.77(c) (1) (i) (*a*), each package shall bear on the outside wrapper or container and the immediate container the statement, "Expiration date _____," the blank being filled in, if it is the aqueous suspension of the drug, with the date that is 18 months (except that the blank may be filled in with the date that is 24 months, if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed for it) or, if it is the dry mixture of the drug, with the date that is 36 months after the month during which the batch was certified.

(d) In addition to complying with the requirements of § 146a.77 (d), a person who requests certification of a batch of benzathine penicillin G and procaine penicillin for aqueous injection shall submit with his request a statement showing the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the procaine penicillin used in making the batch for potency, crystallinity, penicillin K content (unless it is procaine penicillin G) and the penicillin G content if it is procaine penicillin G, and the number of units of procaine penicillin in each milliliter of the batch, if it is the aqueous suspension of the drug, or the number of units of

procaine penicillin in each package of the batch, if it is the dry mixture of the drug. He shall also submit in connection with his request a sample consisting of three packages containing approximately equal portions of not less than 500 milligrams each of the procaine penicillin used in making the batch. If such batch is packaged for repacking, each portion in the sample required by § 146a.77 (d) (4) (i) shall consist of the equivalent of approximately 600 milligrams in lieu of 300 milligrams.

(e) The fees for the services rendered with respect to the samples submitted in accordance with the regulations in this section shall be:

(1) $5.00 for each immediate container in the sample submitted as required by § 146a.77 (d) (4) (i).

(2) $4.00 for each immediate container in the sample of procaine penicillin submitted in accordance with paragraph (d) of this section.

§ 146a.87 Penicillin-bacitracin-neomycin ointment; penicillin-bacitracin-neomycin in oil.

Penicillin-bacitracin-neomycin ointment and penicillin-bacitracin-neomycin in oil conform to all requirements prescribed by § 146a.56 for penicillin-bacitracin ointment and are subject to all procedures prescribed by § 146a.56 for penicillin-bacitracin ointment, except that:

(a) It contains not less than 5.0 milligrams of neomycin and not less than 250 units of bacitracin per gram, unless it is packaged and labeled solely for veterinary use. The neomycin used conforms to the standards prescribed by § 146e.410(a)(2) of this chapter, except the standard for toxicity.

(b) In addition to complying with the requirements of § 146a.56(a)(3), a person who requests certification of a batch of penicillin-bacitracin-neomycin ointment or penicillin-bacitracin-neomycin in oil shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and dates of the latest tests and assays of the neomycin used in making the batch for potency, moisture, and pH. He shall also submit in connection with his request a sample consisting of not less than seven immediate containers of the batch and (unless it was previously submitted) a sample consisting of five packages of the neomycin used in making the batch, containing approximately 0.5 gram each.

(c) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (b) of this section shall be:

(1) $6.00 for each immediate container in the batch.

(2) $4.00 for each immediate container of the neomycin used in making the batch.

§ 146a.88 Penicillin-streptomycin tablets; penicillin-dihydrostreptomycin tablets.

(a) Penicillin-streptomycin tablets and penicillin-dihydrostreptomycin tablets conform to all requirements and are subject to all procedures prescribed by § 146a.27 for penicillin tablets, except that:

(1) Each tablet contains not less than 20 milligrams of streptomycin or dihydrostreptomycin, except if it is intended for use in parakeets and canaries each tablet contains not less than 2.5 milligrams of streptomycin or dihydrostreptomycin and not less than 32,500 units of penicillin. If the tablets are intended for human use, the streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.101(a) or § 146b.103 of this chapter, except the standards for sterility, pyrogens, and histamine content. If the tablets are intended solely for veterinary use, the streptomycin or dihydrostreptomycin used may conform to the standards prescribed by § 146b.114(a) of this chapter.

(2) In lieu of the labeling prescribed for penicillin tablets by § 146a.27(c)(1)(ii), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(3) In addition to complying with the requirements of § 146a.27 (d), a person who requests certification of a batch of penicillin-streptomycin tablets or penicillin-dihydrostreptomycin tablets shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin, and the number of milligrams of streptomycin or dihydrostreptomycin in each tablet of the batch. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of five packages containing approximately equal portions of not less than 0.5 gram each of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101(b) of this chapter.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the regulations in this section shall be:

(1) $1.00 for each tablet submitted in accordance with the requirements of § 146a.27(d)(3)(i)(*a*)(*1*) and (3).

(2) $4.00 for each immediate container in the sample of streptomycin or dihydrostreptomycin submitted in accordance with paragraph (a) (3) of this section.

(c) Exemption of penicillin-streptomycin tablets and penicillin-dihydrostreptomycin tablets for veterinary use from certification: Penicillin-streptomycin tablets and penicillin-dihydrostreptomycin tablets that conform to the requirements of paragraph (a) of this section (except that they may contain one or more essential vitamin and mineral substances for nutritive purposes) shall be exempt from the requirements of sections 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) They are intended solely for veterinary use and are conspicuously so labeled.

(2) If they contain added vitamins or minerals, the labels bear the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear an expiration date that is not more than 18 months after the month during which the batch was last assayed and released by the manufacturer.

(4) The labels bear a statement that solutions prepared with the drugs are stable for not more than 24 hours.

(5) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Chronic respiratory disease (air-sac infection) in chickens.

(ii) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(iii) Bacterial respiratory disease (pneumonia, bronchitis, rhinitis) and bacterial enteritis in parakeets and canaries.

(iv) When intended for use in the conditions named in subdivision (iii) of this subparagraph, the potency must be such that, when used as directed in the labeling, each ounce of drinking water contains 65,000 units of penicillin and 5 milligrams of streptomycin or dihydrostreptomycin for disease prevention, and 130,000 units of penicillin and 10 milligrams of streptomycin or dihydrostreptomycin for use in disease treatment.

§ 146a.89 Penicillin-streptomycin-neomycin in oil; penicillin-dihydrostreptomycin-neomycin in oil; penicillin-streptomycin-neomycin ointment; penicillin-dihydrostreptomycin-neomycin ointment.

Penicillin-streptomycin-neomycin in oil and penicillin-dihydrostreptomycin-neomycin in oil conform to all requirements and are subject to all procedures prescribed by § 146a.57 for procaine penicillin and streptomycin in oil and procaine penicillin and dihydrostreptomycin in oil. Penicillin-streptomycin-neomycin ointment and penicillin-dihydrostreptomycin-neomycin ointment conform to all requirements and are subject to all procedures prescribed by § 146a.54 for penicillin-streptomycin ointment and penicillin-dihydrostreptomycin ointment, except that:

(a) (1) Unless it is intended solely for veterinary use and is conspicuously so labeled, it contains not less than 2.0 milligrams of neomycin per milliliter. The neomycin used conforms to the standards prescribed for neomycin by § 146e.410 (a) (2) of this chapter, except the standard for toxicity (unless it is intended for use by subcutaneous injection in fowl).

(2) If it is intended solely for veterinary use and is conspicuously so labeled, it may contain polyvinylpyrrolidone.

(3) If it is intended solely for veterinary use in the eyes and ears of animals and is conspicuously so labeled, it may contain chlorhexidine dihydrochloride-(bis (p-chlorophenyl-diguanido) hexane dihydrochloride).

(b) (1) Its expiration date shall be 12 months after the month during which the batch was certified, except that the expiration date shall be 18 months or 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(2) On the label and labeling, if it contains polyvinylpyrrolidone or chlorhexidine, after the name "penicillin-streptomycin-neomycin in oil," "penicillin-dihydrostreptomycin-neomycin in oil," "penicillin-streptomycin-neomycin ointment," or "penicillin-dihydrostreptomycin-neomycin ointment," wherever such name appears, the words "with polyvinylpyrrolidone," or "with chlorhexidine dihydrochloride," in juxtaposition with such name.

(c) In addition to complying with the requirements of § 146a.54 (c) or § 146a.57 (a) (4), a person who requests certification of a batch shall submit with his request a statement showing the number of milligrams of neomycin in each milliliter or gram of the batch, the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, toxicity (if it is intended for subcutaneous injection in fowl), moisture,, and pH. He shall also submit in connection with his request a sample consisting of not less than 7 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making such batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (c) of this section shall be:

(1) $6.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of the neomycin used in making the batch.

§ 146a.90 Procaine penicillin and benzathine penicillin G in streptomycin sulfate solution; procaine penicillin and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (procaine penicillin and benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).

Procaine penicillin and benzathine penicillin G in streptomycin sulfate solution and procaine penicillin and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary conform to all requirements and are subject to all procedures prescribed by § 146a.67 for procaine penicillin in streptomycin sulfate solution and procaine penicillin in dihydrostreptomycin sulfate solution veterinary except that:

(a) Each milliliter shall contain not less than 100,000 units of procaine penicillin, not less than 100,000 units of benzathine penicillin G, and not less than 0.25 gram of streptomycin sulfate or dihydrostreptomycin sulfate, but each immediave container shall contain not less than 200,000 units of procaine penicillin, not less than 200,000 units of benzathine penicillin G, and not less than 0.5 gram of streptomycin sulfate or dihydrostreptomycin sulfate. The benzathine penicillin G used conforms to the requirements prescribed by § 146a.68 (a).

(b) In addition to complying with the requirements of § 146a.67(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the benzathine penicillin G used in making the batch for potency, crysallinity, and penicillin G content, and the number of units of benzathine penicillin G in each milliliter of the batch. He shall also submit in connection with his request a sample consisting of 3 packages containing approximately equal portions of not less than 0.5 gram each of the benzathine penicillin G used in making the batch.

(c) The fees for the services rendered with respect to the samples submitted in accordance with the regulations in this section shall be:

(1) $6.00 for each immediate container of the batch submitted in accordance with § 146a.67(d) (3) (i) (*a*) or (4) (i).

(2) $4.00 for each immediate container of benzathine penicillin G submitted in accordance with paragraph (b) of this section.

§ 146a.91 Benzathine penicillin G and streptomycin; benzathine penicillin G and dihydrostreptomycin veterinary.

Benzathine penicillin G and streptomycin and benzathine penicillin G and dihydrostreptomycin veterinary conform to all requirements prescribed by § 146a.77 for the dry mixture of benzathine penicillin G for aqueous injection and are subject to all procedures prescribed by that section for benzathine penicillin G for aqueous injection except that:

(a) It contains not less than 0.5 gram of streptomycin or dihydrostreptomycin for each 100,000 units of benzathine penicillin G.

(b) In addition to complying with the requirements of § 146a.77(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, histamine content, streptomycin content if it is dihydrostreptomycin and crystallinity if it is crystalline dihydrostreptomycin, the number of units of benzathine penicillin G, and the number of grams of streptomycin or dihydrostreptomycin in each immediate container of the batch. He shall also submit in connection with his request a sample consisting of not less than 12 immediate containers of the batch and a sample of the streptomycin or dihydrostreptomycin used in making the batch consisting of 6 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101(b) of this chapter.

(c) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (b) of this section shall be:

(1) $5.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of streptomycin or dihydrostreptomycin used in making the batch.

§ 146a.92 Tablets benzathine penicillin G and crystalline penicillin.

Tablets benzathine penicillin G and crystalline penicillin conform to all requirements prescribed therefor by § 146a.27 for penicillin tablets and are subject to all procedures prescribed by that section for penicillin tablets, except that:

(a) Each tablet contains not less than 100,000 units of benzathine penicillin G and not less than 100,000 units of crystalline penicillin sodium or potassium penicillin.

(b) Their moisture content is not more than 4 percent.

(c) The fee for the services rendered shall be $1.00 for each tablet submitted in accordance with the requirements of § 146a.27(d) (3) (i) (*a*) (*1*) and (3).

§ 146a.93 Penicillin-streptomycin powder; penicillin-dihydrostreptomycin powder.

Penicillin-streptomycin powder and penicillin-dihydrostreptomycin powder conform to all the requirements and are subject to all procedures prescribed by § 146a.88 for penicillin-streptomycin tablets and penicillin-dihydrostreptomycin tablets, except that:

(a) Each gram contains not less than 50,000 units of penicillin (except if it is intended solely for veterinary use each gram contains not less than 2,200 units of penicillin) and not less than 5 milligrams of streptomycin or dihydrostreptomycin.

(b) In lieu of the labeling prescribed by § 146a.88 (a) (2), each package shall bear on the outside wrapper or container and the immediate container the number of units of penicillin and the number of milligrams of streptomycin or dihydrostreptomycin in each gram and the statement "Expiration date _____," the blank being filled in with the date which is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays that show such drug as prepared by him is stable for such period of time.

(c) In lieu of the minimum number of tablets prescribed by § 146a.88 (a) (3), a person who requests certification of a batch shall submit with his request a sample of the batch consisting of 1 im-

mediate container for each 5,000 immediate containers but in no case less than 6 immediate containers. Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(d) The fee for the services rendered with respect to each immediate container in the sample submitted in accordance with the requirements prescribed by paragraph (c) of this section shall be $5.00.

(e) Exemption of penicillin-streptomycin powder and penicillin-dihydrostreptomycin powder for veterinary use from certification: Penicillin-streptomycin powder and penicillin-dihydrostreptomycin powder that conform to the requirements of this section (except that they may contain one or more essential vitamin and mineral substances for nutritive purposes) shall be exempt from the requirements of section 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) They are intended solely for veterinary use and are conspicuously so labeled.

(2) If they contain added vitamins or minerals, the labels bear the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear an expiration date that is not more than 18 months after the month during which the batch was last assayed and released by the manufacturer.

(4) The labels bear a statement that solutions prepared with the drugs are stable for not more than 24 hours.

(5) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Bacterial enteritis in swine.

(ii) Bacterial calf scours.

(iii) Chronic respiratory disease (air-sac infection) in chickens.

(iv) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(v) Infectious sinusitis in poultry.

§ 146..94 Dibenzylamine penicillin G (dibenzylamine penicillin G salt).

(a) *Standards of identity, strength, quality, and purity.* Dibenzylamine penicillin G is the crystalline dibenzylamine salt of penicillin G. It contains not less than 85 percent by weight of the dibenzylamine salt of penicillin G. Each such drug is so purified and dried that:

(1) Its potency is not less than 975 units per milligram.

(2) It is sterile.

(3) It is nontoxic.

(4) It is nonpyrogenic.

(5) Its moisture content is not more than 4.0 percent.

(6) Its pH in saturated aqueous solution is not less than 5.0 and not more than 7.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The weight of the drug and the number of units in the immediate container.

(3) The statement "Expiration date ----------," the blank being filled in with the date which is 18 months after the month during which the batch was certified.

(4) The statement "For manufacturing use only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the weight of the drug and the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH, crystallinity, and the penicillin G content.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 10 packages.

(ii) For sterility test; 10 packages.

Each such package shall contain approximately 300 milligrams taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which dibenzylamine penicillin G is to be used, the manufacturer of a batch that is to be so used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers in the sample submitted in accordance with paragraph (d) (2) (ii) of this section.

(2) If the Commissioner considers that investigations other than the examination of such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.95 Dibenzylamine penicillin and potassium penicillin powder, buffered.

(a) *Standards of identity, strength, quality, and purity.* Dibenzylamine penicillin and potassium penicillin powder, buffered, is a dry mixture of dibenzylamine penicillin G and potassium penicillin G, with or without one or more suitable sulfonamides, and with one or more suitable and harmless buffer substances, colorings, and flavorings. It shall contain not less than 100,000 units of potassium penicillin G for each 200,000 units of dibenzylamine penicillin G. Its moisture content is not more than 1 percent. Its pH is not less than 5.5 and not more than 7.5. The dibenzylamine penicillin G used conforms to the requirements of § 146a.94 (a), except subparagraphs (2) and (4) of that paragraph. The potassium penicillin used conforms to the requirements of § 146a.24 (a) for potassium penicillin, except subparagraphs (2) and (4) of that paragraph. Each other ingredient used, if its name is recognized in the U. S. P. or N. F. conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container the statement "Expiration date ------," the blank being filled in with the date that

is 12 months after the month during which the batch was certified.

(ii) If it contains sulfonamides, after the name "dibenzylamine penicillin and potassium penicillin powder, buffered," wherever it appears, the words "with sulfonamides," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement, "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates on which the latest assays of the dibenzylamine penicillin G and the potassium penicillin G used in making the batch were completed, the number of units of dibenzylamine penicillin G and the number of units of potassium penicillin G in each container of the batch, the date on which the latest assay comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The dibenzylamine penicillin G used in making the batch; potency, toxicity, moisture, pH, crystallinity, and penicillin G content.

(iii) The potassium penicillin G used in making the batch; potency, toxicity, moisture, pH, penicillin G content, crystallinity, and heat stability.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 6 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The dibenzylamine penicillin G used in making the batch; 3 packages, each containing approximately equal portions of not less than 500 milligrams packaged in accordance with the requirements of § 146a.94 (b).

(iii) The potassium penicillin G used in making the batch; 3 packages, each containing approximately equal portions of not less than 250 milligrams packaged in accordance with the requirements of § 146a.24 (b).

(iv) In case of an initial request for certification, each other ingredient used in making the batch; 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) and (iii) of this paragraph, and no sample referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such results or samples have been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.96 Dibenzylamine penicillin and streptomycin in oil; dibenzylamine penicillin and dihydrostreptomycin in oil.

Dibenzylamine penicillin and streptomycin in oil and dibenzylamine penicillin and dihydrostreptomycin in oil conform to all the requirements prescribed by § 146a.57 for procaine penicillin and streptomycin in oil and procaine penicillin and dihydrostreptomycin in oil and are subject to all procedures prescribed by § 146a.57 for procaine penicillin and streptomycin in oil and procaine penicillin and dihydrostreptomycin in oil, except that dibenzylamine penicillin is used in lieu of procaine penicillin. The dibenzylamine penicillin used conforms to the requirements of § 146a.94 (a), except § 146a.94(a) (2), (3) (unless it is intended for subcutaneous injection in fowl), and (4).

§ 146a.97 Hydrabamine penicillin G (hydrabamine penicillin G salt).

(a) *Standards of identity, strength, quality, and purity.* Hydrabamine penicillin G is the crystalline salt N,N'-bis-(dehydroabietyl) ethylenediamine dipenicillin G. It contains not less than 85 percent by weight of the hydrabamine salt of penicillin G. It is so purified and dried that:

(1) Its potency is not less than 845 units per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 2 percent.

(4) Its pH in a saturated aqueous solution is not less than 4.0 and not more than 7.5.

(5) Its extinction coefficient $E^{1\%}_{1\,cm.}$ is not less than 8 at 276 millimicrons.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of units per milligram and the number of grams in the immediate container.

(3) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(4) The statement "For use in the manufacture of nonparenteral drugs only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, crystallinity, the penicillin G content, and extinction coefficient.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of 10 packages, each containing approximately 300 milligrams taken from a different part of such batch, packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.98 Hydrabamine penicillin G oral suspension.

(a) *Standards of identity, strength, quality, and purity.* Hydrabamine penicillin G oral suspension is hydrabamine penicillin G and one or more suitable and harmless suspending or dispersing agents, buffer substances, and preservatives, with or without one or more suitable and harmless colorings and flavorings. Its potency is not less than 60,000 units per milliliter. Its pH is not less than 5.5 and not more than 7.0. The hydrabamine penicillin G used conforms to the requirements of § 146a.97(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Shake well."

(ii) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the hydrabamine penicillin G used in making such batch was completed, the potency per milliliter of the batch, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: average potency per milliliter, pH.

(ii) The hydrabamine penicillin G used in making the batch: potency, toxicity, moisture, pH, crystallinity, the penicillin G content, and the extinction coefficient.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The hydrabamine penicillin G used in making the batch: 10 packages, each containing equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146a.97(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.99 Capsules crystalline penicillin G (capsules crystalline penicillin G potassium, capsules crystalline penicillin G sodium).

(a) *Standards of identity, strength, quality, and purity.* Capsules crystalline penicillin are crystalline penicillin G, sodium or potassium, with or without one or more suitable and harmless buffer substances, vitamin substances, and vegetable oils, and with or without one or more suitable antihistaminics and vasoconstrictors, enclosed in suitable and harmless gelatin capsules. The potency of each capsule is not less than 50,000 units. The moisture content is not more than 1.5 percent unless the person who requests certification has submitted information adequate to prove that his drug is stable for that period of time covered by its expiration date when it has a moisture content of more than 1.5 percent; but in no case shall its moisture content be more than 4.0 percent. The crystalline penicillin G used conforms to the requirements of § 146a.24 (a), except § 146a.24 (a) (2) and (4). Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees.* Capsules crystalline penicillin G conform to all requirements and procedures prescribed for crystalline penicillin G tablets by § 146a.27 (b), (c), (d), and (e), except that:

(1) If it is for use in the preparation of oral solutions, each package shall bear on its outside wrapper or container and the immediate container a statement that contains adequate directions for preparing such solutions and a statement that such solutions should be used immediately.

(2) If it contains vitamin substances, each package shall bear on the outside wrapper or container and the immediate container the name and quantity of each such ingredient.

(3) It shall be labeled with an expiration date that is 12 months, if it contains one or more vitamin substances, or 36 months, if it does not contain one or more vitamin substances, after the month during which the batch was certified, except that the date may be 18 months, 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(4) If it contains one or more vitamin substances, after the name "capsules crystalline penicillin G potassium," or "capsules crystalline penicillin G sodium," wherever either such name appears, the words "with vitamin ------" (the blank being filled in with the name of the vitamin ingredient used) or "with vitamins" (if it contains more than one vitamin ingredient), in juxtaposition with such name.

§ 146a.100 Benzathine penicillin G in oil.

Benzathine penicillin G in oil conforms to all requirements and is subject to all procedures prescribed by § 146a.45 for sterile procaine penicillin in oil, except that:

(a) Benzathine penicillin G is used in lieu of procaine penicillin. The benzathine penicillin used conforms to the requirements of § 146a.68 (a).

(b) Its moisture content is not more than 4 percent.

§ 146a.101 Benzathine penicillin G and procaine penicillin G in oil.

(a) Benzathine penicillin G and procaine penicillin G in oil conforms to all requirements and is subject to all proce-

dures prescribed by § 146a.45 for sterile procaine penicillin in oil, except that:

(1) Each milliliter contains not less than 150,000 units each of benzathine penicillin G and procaine penicillin G, unless it is intended solely for veterinary use and is conspicuously so labeled. The benzathine penicillin G used conforms to the requirements of § 146a.68 (a).

(2) Its moisture content is not more than 4.0 percent.

(3) [Reserved]

(4) In addition to complying with the requirements of § 146a.45 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the benzathine penicillin G used in making the batch for potency, sterility, pyrogens, toxicity, moisture, pH, crystallinity, and penicillin G content, and the number of units each of benzathine penicillin G and procaine penicillin in each milliliter of the batch. He shall also submit in connection with his request a sample consisting of not less than 6 packages of the batch and (unless previously submitted) samples of the benzathine penicillin G used in making the batch, as follows:

(i) For all tests except sterility: 10 packages, each containing approximately equal portions of 300 milligrams.

(ii) For sterility testing: 10 packages, each containing approximately equal portions of 300 milligrams.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(1) $5.00 for each immediate container of the batch submitted in accordance with paragraph (a) (4) of this section.

(2) $4.00 for each immediate container of benzathine penicillin G submitted in accordance with paragraph (a) (4) (i) of this section.

(3) $10.00 for all containers of samples submitted in accordance with paragraph (a) (4) (ii) of this section.

§ 146a.102 Benzathine penicillin G-procaine penicillin G-streptomycin in oil; benzathine penicillin G-procaine penicillin G-dihydrostreptomycin in oil veterinary.

(a) Benzathine penicillin G-procaine penicillin G-streptomycin in oil and benzathine penicillin G-procaine penicillin G-dihydrostreptomycin in oil veterinary conform to all requirements and are subject to all procedures prescribed by § 146a.101 for benzathine penicillin G and procaine penicillin G in oil, except that:

(1) Each milliliter shall contain not less than 250 milligrams of streptomycin or dihydrostreptomycin. The streptomycin used conforms to the standards prescribed by § 146b.101 (a) of this chapter. The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103 of this chapter.

(2) [Reserved]

(3) In addition to complying with the requirements of § 146a.101 (a) (4), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, sterility, toxicity, pyrogens, histamine, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin; and the number of units of benzathine penicillin G and procaine penicillin, and the number of milligrams of streptomycin or dihydrostreptomycin in each milliliter of the batch. He shall also submit in connection with his request a sample consisting of not less than 7 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 5 packages (for all tests except sterility) and 10 packages (for sterility testing), each containing approximately 0.5 gram of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101 (b) of this chapter.

(b) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (a) (3) of this section shall be:

(1) $6.00 for each immediate container of the batch.

(2) $10.00 for each immediate container of the streptomycin or dihydrostreptomycin used in making the batch.

(3) $10.00 for all containers in the samples submitted for sterility testing.

§ 146a.103 Penicillin V (phenoxymethyl penicillin).

(a) *Standards of identity, strength, quality, and purity.* Penicillin V is crystalline phenoxymethyl penicillin. It contains not less than 90 percent of penicillin V. It is so purified and dried that:

(1) Its potency is not less than 1,500 units per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 2.0 percent.

(4) Its pH in a saturated aqueous solution is not less than 2.5 and not more than 4.0.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of units per milligram and the number of grams in the immediate container.

(3) The statement "Expiration date ------," the blank being filled in with the date that is 24 months after the month in which the batch was certified, except that the blank may be filled in with the date that is 36 months or 48 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(4) The statement "For use in the manufacture of nonparenteral drugs only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, crystallinity, and penicillin V content.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of 10 packages, each containing approximately 300 milligrams taken from a different part of such batch, packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.104 Penicillin V for oral suspension (phenoxymethyl penicillin for oral suspension) potassium penicillin V for oral solution.

(a) *Standards of identity, strength, quality, and purity.* Penicillin V for oral suspension or potassium penicillin V for oral solution is a mixture of penicillin V or potassium penicillin V, with or without one or more suitable and harmless suspending agents, coloring, flavorings, buffer substances, and preservatives, and with or without one or more suitable sulfonamides. Its moisture content is not more than 1 percent. The penicillin V used conforms to the requirements of § 146a.103(a). The potassium penicillin V used conforms to the requirements of § 146a.61(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each immediate container may be packaged in combination with a container of a suitable and harmless aqueous vehicle.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that if it contains sulfonamides the blank shall be filled in with the date that is 12 months after the month during which the batch was certified, and except that the blank may be filled in with the date that is 24 months after the month in which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) If it contains sulfonamides, after the name "penicillin V for oral suspension" or "potassium penicillin V for oral solution," wherever such name appears, the words "with sulfonamides," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the penicillin used in making such batch was completed, the number of units in each immediate container, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The penicillin V or potassium penicillin V used in making the batch: Potency, toxicity, moisture, pH, crystallinity, and penicillin V content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The penicillin used in making the batch: 10 packages, each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146a.103 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each, containing approximately 5 grams.

(iv) In case of an initial request for certification of a batch that is to be packaged in combination with an aqueous vehicle, or when any change is made in the composition of such aqueous vehicle: Five packages of the vehicle included in the combination.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.105 Benzathine penicillin V (benzathine penicillin V salt).

(a) *Standards of identity, strength, quality, and purity.* Benzathine penicillin V is the crystalline benzathine salt of penicillin V. It contains not less than 90 percent by weight of the benzathine salt of penicillin V. It is so purified and dried that:

(1) Its potency is not less than 1,050 units per milligram.

(2) It is sterile.

(3) It is nonpyrogenic.

(4) It is nontoxic.

(5) Its moisture content is not more than 8.0 percent.

(6) Its pH in a saturated aqueous solution is not less than 4.0 and not more than 6.5.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of units per milligram and the number of grams in the immediate container.

(3) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(4) The statement "For manufacturing use only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, pyrogens, toxicity, moisture, pH, crystallinity, and penicillin V content.

(2) Each person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility: 10 packages.

(ii) For sterility testing: 10 packages.

Each such package shall contain approximately 300 milligrams, taken from different parts of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which benzathine penicillin V is to be used, the manufacturer of a batch that is to be so used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed in subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this para-

graph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (3) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146a.106 Tablets benzathine penicillin G and penicillin V.

(a) Tablets benzathine penicillin G and penicillin V conform to all requirements and are subject to all procedures prescribed by § 146a.27 for tablets benzathine penicillin G, except that each tablet contains not less than 50,000 units of penicillin V.

(b) In addition to complying with the requirements of § 146a.27(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the penicillin V used in making the batch for potency, toxicity, moisture, pH, crystallinity, and penicillin V content. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 10 packages containing approximately equal portions of not less than 300 milligrams each of the penicillin V used in making the batch, packaged in accordance with the requirements of § 146a.103(b).

(c) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (b) of this section shall be:

(1) $1.00 for each tablet submitted in accordance with the requirements of § 146a.27(d) (3) (i) (*a*) (*1*) and (*3*).

(2) $4.00 for each immediate container of the penicillin V used in making the batch.

§ 146a.107 Capsules penicillin V.

Capsules penicillin V are capsules that conform to all the requirements and are subject to all procedures prescribed by § 146a.27 for tablets penicillin V, except with respect to disintegration time, and except that the moisture content of such capsules is not more than 2 percent.

§ 146a.108 Procaine penicillin-streptomycin-polymyxin in oil; procaine penicillin-dihydrostreptomycin-polymyxin in oil; procaine penicillin-streptomycin-polymyxin ointment; procaine penicillin-dihydrostreptomycin-polymyxin ointment.

Procaine penicillin-streptomycin-polymyxin in oil, procaine penicillin-dihydrostreptomycin-polymyxin in oil, procaine penicillin-streptomycin-polymyxin ointment, and procaine penicillin - dihydrostreptomycin - polymyxin ointment conform to all requirements and are subject to all procedures prescribed by § 146a.54 for procaine penicillin-streptomycin ointment or procaine penicillin-dihydrostreptomycin ointment or by § 146a.57 for procaine penicillin and streptomycin in oil or procaine penicillin and dihydrostreptomycin in oil, except that:

(a) They contain not less than 50,000 units of polymyxin B per single-dose container. The polymyxin B used conforms to the requirements prescribed for polymyxin B by § 146b.107 (a) of this chapter, except the standard prescribed for toxicity (unless it is intended for subcutaneous injection in fowl).

(b) In lieu of the labeling prescribed by § 146a.54(b) or § 146a.57(a) (3), each package shall bear on the outside wrapper or container and the immediate container the statement, "For udder instillation of cattle only"; and the statement, "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that if the person who requests certification has submitted to the Commissioner results of tests and assays that show such drug as prepared by him is stable for 18 months or 24 months, such date may be used for such drug. Each package shall also bear on its label or labeling, if it contains one or more of the active ingredients specified in § 146a.54(a) (3) or § 146a.57(a) (2), after the name "procaine penicillin-streptomycin-polymyxin in oil," "procaine penicillin-dihydrostreptomycin-polymyxin in oil," "procaine penicillin-streptomycin-polymyxin ointment," or "procaine penicillin-dihydrostreptomycin-polymyxin ointment," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of each such ingredient)," in juxtaposition with such name.

(c) In addition to complying with the requirements of § 146a.54 (c) or § 146a.57 (a) (4), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and date of the latest tests and assays of the polymyxin used in making the batch for potency and toxicity. He shall also submit in connection with his request a sample consisting of not less than 7 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 5 packages containing equal portions of not less than 0.5 gram each of the polymyxin used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $6.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of the polymyxin used in making the batch.

§ 146a.109 Benzathine penicillin V oral suspension, benzathine penicillin V for oral suspension.

Benzathine penicillin V oral suspension and benzathine penicillin V for oral suspension conform to all requirements and are subject to all procedures prescribed by § 146a.69 for benzathine penicillin G oral suspension and benzathine penicillin G for oral suspension, except that:

(a) If it is benzathine penicillin V for oral suspension, its pH is not less than 5.0 and not more than 7.0.

(b) Benzathine penicillin V is used in lieu of benzathine penicillin G. The benzathine penicillin V used conforms to the requirements of § 146a.105(a).

(c) In lieu of the directions prescribed by § 146a.69(d) (2) (ii), a person who requests certification of a batch shall submit in connection with his request results of the tests and assays made by him on an accurately representative sample of the benzathine penicillin V used in making the batch for potency, toxicity, pH, mositure, crystallinity, and the penicillin V content.

§ 146a.110 Benzathine penicillin G in streptomycin sulfate solution; benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).

Benzathine penicillin G in streptomycin sulfate solution and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary conform to all requirements and are subject to all procedures prescribed by § 146a.67 for procaine penicillin in streptomycin sulfate solution and procaine penicillin in dihydrostreptomycin sulfate solution veterinary, except that benzathine penicillin G is used in lieu of procaine penicillin. The benzathine penicillin G used conforms to the requirements of § 146a.68 (a).

§ 146a.111 Procaine penicillin-neomycin-polymyxin in oil; procaine penicillin-neomycin-polymyxin ointment.

(a) *Standards of identity, strength, quality, and purity.* Procaine penicillin-neomycin-polymyxin in oil is a suspension of procaine penicillin, neomycin, and polymyxin in refined peanut oil or sesame oil, with or without the addition of one or more suitable and harmless dispersing and suspending agents. Procaine penicillin - neomycin - polymyxin ointment is procaine penicillin, neomycin, and polymyxin in a suitable and harmless ointment base. Each of the drugs may contain a suitable anesthetic, a suitable and harmless preservative, a suitable and harmless salt of cobalt, one or more suitable sulfonamides, and cor-

tisone or a suitable derivative of cortisone. The moisture content of each drug is not more than 1.0 percent. Each drug contains not less than 25,000 units of procaine penicillin, not less than 17.5 milligrams of neomycin, and not less than 5,000 units of polymyxin per milliliter or per gram, except that if the drug is intended for use by udder instillation, each single dose as recommended in its labeling contains not more than 100,000 units of penicillin. The procaine penicillin used conforms to the requirements of § 146a.44 (a), except § 146a.44 (a) (2), (3), and (4). The neomycin used conforms to the requirements of § 146e.410 (a) (2) of this chapter, except the standard for toxicity. The polymyxin used conforms to the requirements of § 146b.107 (a) of this chapter, except the standard for toxicity. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees.* Each drug conforms to all requirements and procedures prescribed for penicillin ointment by § 146a.26 (b) (except that procaine penicillin-neomycin-polymyxin in oil may be packaged in plastic tubes), (c), (d), and (e), except that:

(1) In addition to the labeling prescribed for penicillin ointment by § 146a.26(c), if they contain one or more of the active ingredients specified in paragraph (a) of this section, each package shall bear on the outside wrapper or container and the immediate container, after the name "procaine penicillin-neomycin-polymyxin in oil" or "procaine penicillin-neomycin-polymyxin ointment," wherever it appears, the words "with _____," the blank being filled in with the common or usual name of each such other ingredient, in juxtaposition with such name.

(2) In addition to complying with the requirements of § 146a.26 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the dates of the latest tests and assays of the neomycin (for potency, moisture, and pH) and polymyxin (for potency) used in making the batch; the number of units of penicillin; the number of milligrams of neomycin, and the number of units of polymyxin per milliliter or per gram. He shall also submit in connection with his requests a sample consisting of not less than seven immediate containers of the batch and (unless they were previously submitted) samples consisting of five packages each of the neomycin and polymyxin used in making the batch, each package containing approximately equal portions of not less than 0.5 gram.

(3) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of subparagraph (2) of this paragraph shall be:

(i) $6.00 for each immediate container of the batch.

(ii) $4.00 for each immediate container in the samples of neomycin and polymyxin used in making the batch.

§ 146a.112 Crystalline penicillin-streptomycin-polymyxin-oxytetracycline-carbomycin powder veterinary; crystalline penicillin-dihydrostreptomycin-polymyxin-oxytetracycline-carbomycin powder veterinary.

(a) *Standards of identity, strength, quality, and purity.* Crystalline penicillin-streptomycin-polymyxin-oxytetracycline-carbomycin powder veterinary and crystalline penicillin-dihydrostreptomycin-polymyxin-oxytetracycline-carbomycin powder veterinary are a mixture of crystalline penicillin, streptomycin or dihydrostreptomycin, polymyxin, crystalline oxytetracycline or crystalline oxytetracycline hydrochloride or a combination of these drugs, and crystalline carbomycin, with one or more suitable and harmless diluents. Each immediate container of powder contains not more than 100,000 units of penicillin, not less than 200 milligrams of streptomycin or dihydrostreptomycin, not less than 150,000 units of polymyxin, not less than 425 milligrams of oxytetracycline or oxytetracycline hydrochloride or a combination of these drugs, and not less than 100 milligrams of carbomycin. Its moisture content is not more than 6.0 percent. The crystalline penicillin used conforms to the standards prescribed therefor by § 146a.24, except § 146a.24(a) (2), (3), and (4). The streptomycin used conforms to the standards prescribed therefor by § 146b.101(a) of this chapter, except § 146b.101(a) (2), (3), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103 of this chapter, except the standards for sterility, toxicity, pyrogens, and histamine. The polymyxin B used conforms to the standards prescribed therefor by § 146b.107(a) of this chapter, except the standard for toxicity. The oxytetracycline used is produced by the growth of Streptomyces Rimosus. The crystalline oxytetracycline base has a potency of not less than 900 micrograms per milliliter on the anhydrous basis, has a moisture content of not more than 7.5 percent, and a pH of from 5.5 to 7.5. The crystalline oxytetracycline hydrochloride has a potency of not less than 835 micrograms per milligram, a moisture content of not more than 1.5 percent, and a pH of from 2.3 to 2.9. The crystalline carbomycin used is produced by the growth of Streptomyces halstedii, has a potency of not less than 750 μg. per milligram, and has a moisture content of not more than 5.0 percent and a pH of from 5.0 to 8.0. Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. The composition of the immediate containers shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of units of penicillin; the number of milligrams of streptomycin or dihydrostreptomycin; the number of units of polymyxin; the number of milligrams of oxytetracycline, oxytetracycline hydrochloride, or the number of milligrams of each such drug where a combination of these two drugs is used; and the number of milligrams of carbomycin, in each gram of the batch.

(iii) The statement "For udder instillation of cattle only."

(iv) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified: *Provided, however,* That such expiration date may be omitted from the immediate container if it contains a single dose and it is packaged in an individual wrapper or container.

(v) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates of the latest tests and assays of the penicillin, streptomycin or dihydrostreptomycin, polymyxin, oxytetracycline, oxytetracycline hydrochloride, and carbomycin used in making the batch.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The penicillin used in making the batch: Potency, moisture, pH, crystallinity, and heat stability.

(iii) The streptomycin or dihydrostreptomycin used in making the batch: Potency, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(iv) The polymyxin used in making the batch: Potency.

(v) The oxytetracycline and oxytetracycline hydrochloride used in making the batch: Potency, moisture, pH, and crystallinity.

(vi) The carbomycin used in making the batch: Potency, moisture, pH, and crystallinity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection

with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 package for each 5,000 packages in the batch, but in no case less than 6 packages.

(ii) The penicillin used in making the batch: 10 packages each containing equal portions of not less than 60 milligrams.

(iii) The streptomycin or dihydrostreptomycin used in making the batch: 6 packages each containing approximately equal portions of not less than 0.5 gram.

(iv) The polymyxin used in making the batch: 5 packages each containing approximately equal portions of not less than 0.5 gram.

(v) The oxytetracycline used in making the batch: 5 packages of each salt used, each containing approximately equal portions of not less than 0.5 gram.

(vi) The carbomycin used in making the batch; 5 packages each containing approximately equal portions of not less than 0.5 gram.

(vii) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii), (iii), (iv), (v), and (vi) of this paragraph, and no samples referred to in subparagraph (3) (ii), (iii), (iv), (v), and (vi) of this paragraph, is required if such result or samples have been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $6.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), (v), (vi), and (vii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

PART 146b—CERTIFICATION OF STREPTOMYCIN (OR DIHYDROSTREPTOMYCIN) AND STREPTOMYCIN- (OR DIHYDROSTREPTOMYCIN-) CONTAINING DRUGS

Sec.

146b.101 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride (streptomycin calcium chloride complex).

146b.102 Streptomycin ointment; dihydrostreptomycin ointment.

146b.103 Dihydrostreptomycin sulfate, crystalline dihydrostreptomycin sulfate, dihydrostreptomycin hydrochloride.

146b.104 Streptomycin tablets; dihydrostreptomycin tablets.

146b.105 Streptomycin for topical use; streptomycin with ——— (the blank being filled in with the name of the vehicle if a package combination) for topical use.

146b.106 Streptomycin sulfate solution; dihydrostreptomycin sulfate solution (crystalline dihydrostreptomycin sulfate solution).

146b.107 Streptomycin-polymyxin-bacitracin tablets.

146b.108 Streptomycin syrup; streptomycin in gel (streptomycin oral suspension); dihydrostreptomycin syrup; dihydrostreptomycin in gel (dihydrostreptomycin oral suspension).

146b.109 Streptomycin - bacitracin - polymyxin gauze pads.

146b.110 Streptomycin otic with antifungal agent; streptomycin otic with ———; dihydrostreptomycin otic with antifungal agent; dihydrostreptomycin otic with ——— (the blank being filled in with the common or usual name of the antifungal agent).

146b.111 Streptomycin - kaolin-pectin - aluminum hydroxide gas powder veterinary; dihydrostreptomycin-kaolin-pectin-aluminum hydroxide gel powder veterinary.

146b.112 Streptomycin for inhalation therapy; dihydrostreptomycin for inhalation therapy.

146b.113 Dihydrostreptomycin-streptomycin sulfates.

146b.114 Streptomycin sulfate veterinary; dihydrostreptomycin sulfate veterinary; dihydrostreptomycin hydrochloride veterinary.

146b.115 Streptomycin sulfate powder oral veterinary; streptomycin sulfate granules oral veterinary; dihydrostreptomycin sulfate powder oral veterinary; dihydrostreptomycin sulfate granules oral veterinary; dihydrostreptomycin hydrochloride powder oral veterinary; dihydrostreptomycin hydrochloride granules oral veterinary.

146b.116 Streptonicozid sulfate.

146b.117 Dihydrostreptomycin-streptomycin sulfates solution.

146b.118 Streptomycin-penicillin - sulfonamide with kaolin and pectin; dihydrostreptomycin-penicillin - sulfonamide with kaolin and pectin.

146b.119 Streptomycin hydrochloride solution oral veterinary; streptomycin sulfate solution oral veterinary.

146b.120 Dihydrostreptomycin-streptomycin sulfates with isonicotinic acid hydrazine.

146b.121 Streptomycin-erythromycin ointment.

146b.122 Streptomycin - chlortetracycline - chloramphenicol-bacitracin dental cement; dihydrostreptomycin - chlortetracycline - chloramphenicol-bacitracin dental cement.

146b.123 Streptomycin - sodium sulfathiazole solution veterinary; dihydrostreptomycin-sodium sulfathiazole solution veterinary.

146b.124 Streptomycin - polymyxin - neomycin ointment; dihydrostreptomycin - polymyxin - neomycin ointment.

146b.125 Streptomycin - dihydrostreptomycin for inhalation therapy.

146b.126 Streptomycin - neomycin powder; dihydrostreptomycin - neomycin powder.

146b.127 Streptomycin solution for inhalation therapy veterinary; dihydrostreptomycin solution for inhalation therapy veterinary.

146b.128 Streptomycin-polymyxin in gel; dihydrostreptomycin-polymyxin in gel.

146b.129 Streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary.

146b.130 Streptomycin and para-aminobenzoic acid powder for inhalation therapy; dihydrostreptomycin and para-aminobenzoic acid powder for inhalation therapy.

146b.131 Streptomycin-polymyxin tablets; dihydrostreptomycin-polymyxin tablets.

146b.132 Streptomycin-neomycin for inhalation therapy veterinary; dihydrostreptomycin-neomycin for inhalation therapy veterinary.

146b.133 Dihydrostreptomycin - neomycin - polymyxin aerosol solution veterinary.

AUTHORITY: §§ 146b.101 to 146b.133 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 146b.101 Streptomycin sulfate, streptomycin hydrochloride, streptomycin phosphate, streptomycin trihydrochloride calcium chloride (streptomycin calcium chloride complex).

(a) *Standards of identity, strength, quality, and purity.* Streptomycin sulfate is the sulfate salt of a kind of streptomycin or a mixture of two or more such salts; streptomycin hydrochloride is the hydrochloride salt of a kind of streptomycin or a mixture of two or more such salts; streptomycin phosphate is the phosphate salt of a kind of streptomycin or a mixture of two or more such salts; streptomycin trihydrochloride calcium chloride is the double salt of a kind of streptomycin or a mixture of two or more such salts. Each such drug is so purified and dried that:

(1) Its potency is not less than 650 micrograms per milligram;

(2) It is sterile;

(3) It is nontoxic;

(4) It is nonpyrogenic;

(5) It contains no histamine or histamine-like substances;

(6) Its moisture content is not more than 5.0 percent;

(7) Its pH in aqueous solution of 0.3 gram per millimeter is not less than 4.5 and not more than 7.0.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of

colorless (unless it is intended solely for veterinary use) transparent glass closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Unless it is intended solely for veterinary use and is conspicuously so labeled, each such container shall contain 0.5 gram, 1.0 gram, 2.0 grams, 3.0 grams, 4.0 grams, 5.0 grams, or 10.0 grams, and each may be packaged in combination with a container of the solvent water for injection U. S. P., dextrose injection 5 percent U. S. P. or physiological salt solution U. S. P.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement, "Expiration date _____," the blank being filled in with the date that is 48 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such a period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) On the circular or other labeling within or attached to the package, if it is packaged for dispensing, the conditions under which such solutions should be stored, including the statement, "Sterile solutions may be stored at room temperature for 4 weeks without significant loss of potency."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(3) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The potency per gram and the number of grams in the immediate container.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The information required by subparagraph (1) (i) of this paragraph.

(d) ***Request for certification, check tests and assays; samples.*** (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of grams in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, histamine content, moisture, pH, and identity. If such batch or any part thereof is to be packaged with a solvent such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) If such batch is packaged for dispensing, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 5 immediate containers.

(ii) For sterility testing; 10 immediate containers.

Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(3) If such batch is packaged for repacking or for use as an ingredient in the manufacture of another drug, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 5 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 0.5 gram taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(4) In connection with contemplated requests for certification of repackaged batches or batches of another drug in the manufacture of which it is to be used, the manufacturer of a batch which is to be so repacked or used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (3) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $10.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i), (3) (i), and (4) of this section; $10.00 for all samples submitted in accordance with paragraph (d) (2) (ii) and (3) (i) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.102 Streptomycin ointment; dihydrostreptomycin ointment.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin ointment and dihydrostreptomycin ointment are streptomycin or dihydrostreptomycin in a suitable and harmless ointment base, with or without suitable and harmless dispersing and suspending agents and preservatives. Their potency is not less than 5,000 μg. per gram of ointment. The streptomycin used conforms to the requirements of § 146b.101 (a), except § 146b.101 (a) (2), (3), (4), (5), and (6). The dihydrostreptomycin used conforms to the requirements of § 146b.103, except the standards for sterility, toxicity, pyrogens, histamine, and moisture. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Streptomycin ointment and dihydrostreptomycin ointment shall be packaged in collapsible tubes which shall be well-closed containers as defined by the U. S. P., and each such tube shall not be larger than the 2-ounce size, except if it is labeled solely for hospital use it may be packaged in immediate containers of glass which meet the test for tight containers as defined by the U. S. P. The composition of the immediate container and closure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of streptomycin ointment or dihydrostreptomycin ointment shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the streptomycin used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that each component of the ointment base used conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: potency, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers unless each such container is packaged for hospital use and contains more than 2 ounces, in which case the sample shall consist of approximately 1 ounce of ointment for each 5,000 immediate containers in the batch, but in no case less than five 1-ounce portions. Such sample shall be collected by taking single immediate containers or 1-ounce portions at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; 5 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) In case of an initial request for certification, the ingredients used in making the ointment base of the batch; one package of each containing approximately 200 grams, except for the suspending and dispersing agents used, in which case the sample shall consist of approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of streptomycin ointment or dihydrostreptomycin ointment under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.103 Dihydrostreptomycin sulfate, crystalline dihydrostreptomycin sulfate, dihydrostreptomycin hydrochloride.

(a) Dihydrostreptomycin sulfate is the hydrogenated sulfate salt of a kind of streptomycin or a mixture of two or more such salts; crystalline dihydrostreptomycin sulfate is the hydrogenated crystalline sulfate salt of a kind of streptomycin or a mixture of two or more such salts; dihydrostreptomycin hydrochloride is the hydrogenated hydrochloride salt of a kind of streptomycin or a mixture of two or more such salts. Each such drug conforms to all requirements prescribed by § 146b.101 for streptomycin sulfate and streptomycin hydrochloride, and is subject to all procedures prescribed by § 146b.101 for streptomycin sulfate and streptomycin hydrochloride, except that:

(1) Its potency is not less than 650 micrograms per milligram, except that if it is crystalline dihydrostreptomycin sulfate its potency is not less than 725 micrograms per milligram.

(2) Its content of streptomycin sulfate or streptomycin hydrochloride is not more than 3.0 percent when calculated as streptomycin base, except that if it is crystalline dihydrostreptomycin sulfate its content of streptomycin sulfate is not more than 1.0 percent.

(b) If it is intended for human parenteral use, in addition to the labeling prescribed for streptomycin sulfate by § 146b.101(c), its labeling shall bear, as hereinafter indicated, the following:

(1) On the outside wrapper or container and on the immediate container the statement, "Warning: For use only in patients who cannot tolerate streptomycin."

(2) On the circular or other labeling within or attached to the package, warnings to the effect that:

(i) Because of its potentiality for causing delayed deafness, dihydrostreptomycin should be administered only to patients having infections that are amenable to treatment with dihydrostreptomycin or streptomycin but for whom streptomycin is contraindicated.

(ii) Severe auditory impairment has been reported following a total parenteral dose of as little as 2 grams to 5 grams of dihydrostreptomycin. The auditory damage, which is usually permanent, may be delayed for a few weeks or up to several months.

§ 146b.104 Streptomycin tablets; dihydrostreptomycin tablets.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin tablets and dihydrostreptomycin tablets are streptomycin or dihydrostreptomycin tableted with or without glucoronolactone, kaolin, or other suitable and harmless absorbent ingredients, pectin, and dried aluminum hydroxide gel, with or without bismuth glycolylarsanilate and one or more suitable sulfonamides, and with or without the addition of one or more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. If it is intended solely for veterinary use and is conspicuously so labeled, it may contain vitamin A. The potency of each tablet is not less than 50 milligrams. Its moisture content is not more than 10 percent. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. If the tablets are intended for human use, the streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.101(a) or § 146b.103, except the standards for sterility, pyrogens, and histamine content. If the tablets are intended solely for veterinary use, the streptomycin or dihydrostreptomycin used may conform to the standards prescribed by § 146b.114(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a well closed container or a tight container as defined by the U. S. P. and it may contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months or 48 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed in paragraph (a) of this section.

(ii) If it contains, in addition to streptomycin or dihydrostreptomycin, one or more of the other active ingredients

specified in paragraph (a) of this section, after the name "streptomycin tablets" or "dihydrostroptomycin tablets," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of each such other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of streptomycin or dihydrostreptomycin tablets shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the streptomycin or dihydrostreptomycin used in making such batch was completed, the potency of each tablet, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per tablet, average moisture, and if required by paragraph (a) of this section, disintegration time.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For potency and moisture: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets, collected by taking single tablets throughout the entire time of tableting so that the quantities tableted during the intervals are approximately equal.

(*b*) For disintegration time: 6 tablets.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; five packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the service rendered with respect to each batch of streptomycin or dihydrostreptomycin tablets under the regulations in this part shall be:

(1) $0.75 for each tablet in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $3.00 for all tablets submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such tablets and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.105 Streptomycin for topical use; streptomycin with _____ (the blank being filled in with the name of the vehicle if a package combination) for topical use.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin for topical use conforms to all the requirements prescribed by § 146b.101 (a) for streptomycin, and may be packaged in combination with a container of a suitable and harmless vehicle.

(b) *Packaging.* The immediate container of streptomycin for topical use shall be of colorless transparent glass so closed as to be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that its contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not less than 20 milligrams.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its outside label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement, "Expiration date _____," the blank being filled in with the date that is 48 months after the month during which the batch was certified.

(ii) If it is a packaged combination, on the immediate container of the vehicle in the combination, a statement giving the method of dissolving the streptomycin in the vehicle and the statement "The solution may be stored at room temperature for 1 week without significant loss of potency."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of streptomycin for topical use shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the number of milligrams in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, histamine content, moisture, and pH. If such batch, or any part thereof, is to be packaged with a vehicle, such request shall be accompanied by a statement that such vehicle conforms to the requirements prescribed therefor by this section.

(2) Such person shall submit in connection with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 50 immediate containers.

(ii) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers, before or after labeling, at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(3) In case of an initial request for the certification of a batch of streptomycin for topical use which is to be packaged in combination with a container of a vehicle, or when any change is made in the composition of such vehicle, such person shall submit in connection with his request five packages of the vehicle included in the combination.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $1.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) (i) of this section; $4.00 for each package in the sample submitted in accordance with paragraph (d) (3) of this section; $10.00

for all containers submitted in accordance with paragraph (d)(2)(ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.106 Streptomycin sulfate solution; dihydrostreptomycin sulfate solution (crystalline dihydrostreptomycin sulfate solution).

(a) *Standards of identity, strength, quality, and purity.* Streptomycin sulfate solution is an aqueous solution of streptomycin sulfate. Dihydrostreptomycin sulfate solution is an aqueous solution of dihydrostreptomycin sulfate or crystalline dihydrostreptomycin sulfate. Such solution conforms to all standards prescribed by § 146b.101 for streptomycin sulfate or § 146b.103 for dihydrostreptomycin sulfate or crystalline dihydrostreptomycin sulfate, except the limitation on moisture content, and except that:

(1) Its potency is not less than 250 milligrams per milliliter and not more than 500 milligrams per milliliter, unless it is intended solely for veterinary use and is conspicuously so labeled.

(2) It contains one or more suitable and harmless preservatives.

(3) Its pH is not less than 5.0 and not more than 8.0.

(4) It may contain one or more suitable and harmless buffer substances and stabilizing agents.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing it shall be in immediate containers of colorless (unless it is intended solely for veterinary use) transparent glass closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness, unless it is packaged to contain a single dose. Each such container shall contain not less than 1.0 milliliter and not more than 50 milliliters, unless it is intended solely for veterinary use and is conspicuously so labeled.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement, "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified except that the blank may be filled in with the date that is 18 months, 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such time period such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(*b*) If it is dihydrostreptomycin sulfate solution, the statement, "*Warning*—For use only in patients who cannot tolerate streptomycin."

(ii) On the outside wrapper or container the statement, "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)," unless the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section after having been stored at room temperature.

(iii) On the circular or other labeling within or attached to the package, if it is dihydrostreptomycin sulfate solution and it is intended for parenteral use, warnings containing information to the effect that:

(*a*) Because of the potentiality for causing delayed deafness, dihydrostreptomycin should be administered only to patients having infections that are amenable to treatment with dihydrostreptomycin or streptomycin, but for whom streptomycin is contraindicated.

(*b*) Severe auditory impairment has been reported following a total parenteral dose of as little as 2 grams to 5 grams of dihydrostreptomycin. The auditory damage, which is usually permanent, may be delayed for a few weeks or up to several months.

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) (i) (*a*) and (ii) of this paragraph except that in lieu of the statement, "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(3) *It is packaged for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The number of milligrams in each milliliter and the number of milliliters in the immediate container.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The information required by subparagraph (1) (i) (*a*) and (1) (ii) of this paragraph.

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of milligrams or grams dissolved in each of such packages, the date on which the latest assay of the drug comprising such batch was completed, and if it is crystalline dihydrostreptomycin sulfate solution, the batch mark and (unless it was previously submitted) the date on which the latest assay of the crystalline dihydrostreptomycin sulfate used in making such batch was completed.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, toxicity, pyrogens, histamine content, pH, and streptomycin content, if it is dihydrostreptomycin sulfate or crystalline dihydrostreptomycin sulfate.

(ii) The streptomycin sulfate or dihydrostreptomycin sulfate used in making the batch; potency on dry basis and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch, if packaged for dispensing:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 5 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The batch, if packaged for repacking or for use in the manufacture of another drug:

(*a*) For all tests except sterility; 5 packages.

(*b*) For sterility testing; 10 packages. Each such package shall contain approximately 2 milliliters taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(iii) The streptomycin or dihydrostreptomycin used in making the batch; one immediate container, unless it is crystalline dihydrostreptomycin, in which case the sample shall consist of three immediate containers. Each im-

mediate container shall contain approximately 0.5 gram of the dried drug packaged in accordance with the requirements of § 146b.101(b). If the streptomycin or dihydrostreptomycin used in making the batch is a solution of the drug, the person who requests certification shall dry a sufficient quantity of such solution for potency testing on the dry basis.

(iv) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (iii) of this paragraph, is required if such result or sample has been previously submitted.

(5) In connection with contemplated requests for certification of repackaged batches or batches of another drug in the manufacture of which it is to be used, the manufacturer of the batch which is to be so repacked or used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (3) (ii) of this paragraph. From the information required by subparagraph (2) (i) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with regard to each batch under the regulations in this part shall be:

(1) $10.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii) (*a*), and (5) of this section; $4.00 for each package in the sample submitted in accordance with paragraph (d) (3) (iii) and (iv) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.107 Streptomycin-polymyxin-bacitracin tablets.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-polymyxin-bacitracin tablets are tablets composed of streptomycin, polymyxin B, and bacitracin, with or without the addition of one or more suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings. The potency of each tablet is not less than 250 milligrams of streptomycin, 200,000 units of polymyxin B, and 5,000 units of bacitracin. Its moisture content is not more than 3 percent. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. The streptomycin used conforms to the standards prescribed therefor by § 146b.101(a), except § 146b.101 (a) (2), (4), and (5). The polymyxin used is produced by the growth of *Bacillus polymyxa*, has a potency of not less than 3,800 units per milligram, and is nontoxic. The bacitracin used conforms to the standards prescribed therefor by § 146e.401 (a) of this chapter, except § 146e.401 (a) (2), (4), and (8). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each tablet is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement, "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of streptomycin-polymyxin-bacitracin tablets shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates on which the latest assays of the streptomycin, polymyxin, and bacitracin used in making such batch were completed, the potency of each tablet, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per tablet, average moisture, and if required by paragraph (a) of this section, disintegration time.

(ii) The streptomycin used in making the batch; potency, toxicity, moisture, and pH.

(iii) The polymyxin used in making the batch; potency and toxicity.

(iv) The bacitracin used in making the batch; potency, toxicity, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For potency and moisture: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets, collected by taking single tablets throughout the entire time of tableting so that the quantities tableted during the intervals are approximately equal.

(*b*) For disintegration time: 6 tablets.

(ii) The streptomycin used in making the batch; five packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) The polymyxin used in making the batch; five packages, each containing approximately equal portions of not less than 0.5 gram.

(iv) The bacitracin used in making the batch; six packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146e.401 (b) of this chapter.

(v) In case of an initial request for certification, each other ingredient used in making the batch; one package of each, containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii), (iii), and (iv) of this paragraph, and no sample referred to in subparagraph (3) (ii), (iii), and (iv) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of streptomycin-polymyxin-bacitracin tablets under the regulations in this part shall be:

(1) $1.00 for each tablet in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $3.00 for all tablets submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), and (v) of this section.

(2) If the Commissioner considers that investigations, other than examina-

tion of such tablets and packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.108 Streptomycin syrup; streptomycin in gel (streptomycin oral suspension); dihydrostreptomycin syrup; dihydrostreptomycin in gel (dihydrostreptomycin oral suspension).

(a) *Standards of identity, strength, quality, and purity.* Streptomycin syrup and dihydrostreptomycin syrup are streptomycin or dihydrostreptomycin dissolved in a suitable and harmless diluent that contains one or more suitable and harmless preservatives. Streptomycin in gel and dihydrostreptomycin in gel are streptomycin or dihydrostreptomycin dissolved or suspended in a suitable and harmless gel base that contains a suitable and harmless adsorbent and one or more suitable and harmless preservatives. Each such drug may contain one or more suitable and harmless suspending or dispersing agents, flavorings, pectin, bismuth glycolylarsanilate, bismuth magma, or bismuth subcarbonate, suitable mineral salts, procaine hydrochloride, a suitable antispasmodic agent, and one or more suitable sulfonamides. Its potency is not less than 10 milligrams per milliliter. The streptomycin used conforms to the standards prescribed therefor by § 146b.101 (a), except subparagraphs (2), (4), (5), and (6) of that paragraph. The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103 except the standards for sterility, pyrogens, moisture, and histamine content. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be glass, so closed as to be a tight container as defined by the U. S. P. and of such composition that will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label and labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement, "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months or 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) If it contains, in addition to streptomycin or dihydrostreptomycin, one or more of the other active ingredients specified in paragraph (a) of this section, after the name "streptomycin syrup," "streptomycin in gel," "dihydrostreptomycin syrup," or "dihydrostreptomycin in gel," wherever such name appears, the words "with _____ (the blank being filled in with the common or usual name of each such other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph except that in lieu of the statement, "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the streptomycin or dihydrostreptomycin used in making the batch was completed, the potency per milliliter of the batch, the quantity of each ingredient used in making the batch, the date on which the latest assay comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per milliliter.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; potency, toxicity, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; five packages containing approximately equal portions of not less than 0.5 gram each packaged in accordance with the requirements of § 146b.101 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section; and

(2) If the Commissioner considers that investigations other than examinations of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.109 Streptomycin-bacitracin-polymyxin gauze pads.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-bacitracin-polymyxin gauze pads are absorbent gauze that is impregnated with streptomycin, bacitracin, and polymyxin B. Each square inch of such pad shall contain not less than 1 milligram of streptomycin, 50 units of bacitracin, and 1,000 units of polymyxin B. It is sterile. Its moisture content is not more than 5 percent. The streptomycin used conforms to the standards prescribed therefor by § 146b.101(a), except subparagraphs (2), (4), and (5) of that paragraph. The bacitracin used conforms to the standards prescribed therefor by § 146e.401(a), except § 146e.401(a) (2), (4), and (8). The polymyxin used conforms to the standards prescribed therefor by § 146b.107 (a). The absorbent gauze used conforms to the standards prescribed therefor by the U. S. P.

(b) *Packaging.* Unless it is intended solely for hospital use, and is conspicuously so labeled, each streptomycin-bacitracin-polymyxin gauze pad shall be packaged individually. In all cases the immediate container shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark;

(ii) The number of milligrams of streptomycin in each pad of the batch;

(iii) The number of units of bacitracin in each pad of the batch;

(iv) The number of units of polymyxin B in each pad of the batch;

(v) The length, width, and type of gauze contained in the pad; and

(vi) The statement "Expiration date ----------," the blank being filled in with the date which is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date which is 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section: *Provided, however,* That such expiration date may be omitted from the immediate container if such immediate container is packaged in an individual wrapper or container.

(2) On the immediate container, the statement "Sterility of the pad cannot be guaranteed if the package bears evidence of damage or has been previously opened."

(3) On the circular or other labeling within or attached to the package, directions and precautions adequate for the use of such pads.

(d) *Request for certification; samples.* (1) In addition to complying with requirements of § 146.2 of this chapter, a person who requests certification of a batch of streptomycin-bacitracin-polymyxin gauze pads shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch marks and (unless they were previously submitted) the dates on which the latest assays of the streptomycin, bacitracin, and polymyxin used in making such batch were completed, the potency of each pad in the batch, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that the absorbent gauze used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency of streptomycin, bacitracin, and polymyxin per pad, sterility, and average moisture.

(ii) The streptomycin used in making the batch; potency, toxicity, moisture, pH, and ash content.

(iii) The bacitracin used in making the batch; potency, toxicity, moisture, and pH.

(iv) The polymyxin used in making the batch; potency and toxicity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one pad for each 5,000 pads in the batch, but in no case less than 30 pads.

(*b*) For sterility testing; 10 pads.

Such samples shall be collected by taking single pads at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin used in making the batch; six packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146b.101 (b).

(iii) The bacitracin used in making the batch; six packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146e.401 (b) of this chapter.

(iv) The polymyxin used in making the batch; five packages, each containing approximately equal portions of not less than 0.5 gram.

(v) In case of an initial request for certification, one package consisting of approximately 5 linear yards, or the equivalent, of the absorbent gauze used.

(4) No result referred to in subparagraph (2) (ii), (iii), and (iv) of this paragraph, and no sample referred to in subparagraph (3) (ii), (iii), and (iv) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $1.00 for each pad in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), and (v) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such pads and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.110 Streptomycin otic with antifungal agent; streptomycin otic with ----------; dihydrostreptomycin otic with antifungal agent; dihydrostreptomycin otic with ---------- (the blank being filled in with the common or usual name of the antifungal agent).

(a) *Standards of identity, strength, quality, and purity.* Streptomycin otic with antifungal agent or dihydrostreptomycin otic with antifungal agent is streptomycin or dihydrostreptomycin and one or more suitable antifungal agents and buffer substances, with or without one or more suitable and harmless preservatives, dissolved or suspended in a suitable and harmless vehicle. Its potency is not less than 2.5 milligrams per milliliter. Its pH is not less than 4.8 and not more than 6.0. The streptomycin used conforms to the standards prescribed therefor by § 146b.101(a), except § 146b.101(a) (2), (3), (4), (5), and (6). The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103 (a), except the standards for sterility, pyrogens, toxicity, histamine, and moisture. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be glass, so closed as to be a tight container as defined by the U. S. P., and of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package will bear on the outside wrapper or container and the immediate container the statement "Expiration date ----------," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph except that in lieu of the statement, "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the streptomycin or dihydrostreptomycin used in making the batch was completed, the potency per milliliter of the batch, the date on which the latest assay of the drug comprising such batch was completed, the quantity

of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per milliliter, pH.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; potency, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; 6 packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146b.101 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.111 Streptomycin-kaolin-pectin-aluminum hydroxide gel powder veterinary; dihydrostreptomycin-kaolin-pectin-aluminum hydroxide gel powder veterinary.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-kaolin-pectin-aluminum hydroxide gel powder veterinary and dihydrostreptomycin-kaolin-pectin aluminum hydroxide gel powder veterinary are streptomycin or dihydrostreptomycin, kaolin, pectin, and dried aluminum hydroxide gel, with or without the addition of one or more suitable and harmless diluents, colorings, and flavorings. Its content of streptomycin or dihydrostreptomycin is not less than 37.5 milligrams per gram of powder. Its moisture content is not more than 10 percent. The streptomycin used conforms to the standards prescribed therefor by § 146b.101 (a), except § 146b.101 (a) (2), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103, except the standards for sterility, pyrogens, and histamine content. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear, on its label or labeling as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of streptomycin or dihydrostreptomycin per gram in the immediate containers.

(iii) The quantity of kaolin, pectin, and aluminum hydroxide per gram in the immediate container.

(iv) The statement "Expiration date ----------," the blank being filled in with the date which is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date which is 24 months, 36 months, or 48 months after the month in which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(v) The statement "For veterinary use only."

(2) On the circular or other labeling within or attached to the package, directions and precautions adequate for the use of such powder, including:

(i) Clinical indications.

(ii) Dosage and administration.

(iii) Contraindications.

(iv) Untoward effects that may accompany administration.

If two or more such immediate containers are in such package, the number of circulars or other labeling shall not be less than the number of such containers.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the streptomycin or dihydrostreptomycin used in making such batch was completed, the potency per gram of powder, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per gram of powder and average moisture.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 containers in the batch, but in no case less than 20 such containers, unless each such container is packaged to contain more than 1.0 gram, in which case the sample shall consist of 1.0 gram for each 5,000 immediate containers in the batch, but in no case less than 20 grams. Such samples shall be collected by taking single immediate containers or 1.0-gram portions at such intervals throughout the entire time the containers are being filled that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; 5 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5.0 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the service rendered with respect to each batch under the regulations in this part shall be:

(1) $1.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146b.112 Streptomycin for inhalation therapy; dihydrostreptomycin for inhalation therapy.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin for inhalation therapy and dihydrostreptomycin for inhalation therapy are streptomycin or dihydrostreptomycin, with or without one or more suitable and harmless diluents. If it is intended for human use, the streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.101(a) or § 146b.103, except the standards for sterility and pyrogens, and except that if it is packaged with inert gases its moisture content is not more than 0.5 percent. If it is intended solely for veterinary use, the streptomycin or dihydrostreptomycin used may conform to the standards prescribed by § 146b.114(a), except that if it is packaged with inert gases its moisture content is not more than 0.5 percent. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container of streptomycin for inhalation therapy and dihydrostreptomycin for inhalation therapy shall be a tight container as defined by the U. S. P.; its closure shall be one through which a hypodermic needle cannot be introduced; and the container shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not less than 50 milligrams, and may contain one or more suitable and harmless inert gases or each may be packaged in combination with a container of a suitable and harmless solvent.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date ----------," the blank being filled in with the date that is 24 months, if it is packaged with inert gases, or 48 months after the month during which the batch was certified; except that if it is packaged with inert gases the blank may be filled in with the date that is 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) The statement "*Warning*—Not for injection."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of streptomycin for inhalation therapy or dihydrostreptomycin for inhalation therapy shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of milligrams in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency and moisture if the streptomycin or dihydrostreptomycin has been previously submitted, or for potency, toxicity, moisture, pH, histamine content (unless it is intended solely for veterinary use), streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin, if the streptomycin or dihydrostreptomycin has not been previously submitted. If such batch, or any part thereof, is to be packaged in combination with a container of a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Such person shall submit with his request accurately representative samples of the following:

(i) The batch:

(*a*) If the streptomycin or dihydrostreptomycin used has been previously submitted: One immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, or if it is packaged with inert gases not less than 7 immediate containers.

(*b*) If the streptomycin or dihydrostreptomycin used has not been previously submitted: One immediate container for each 5,000 immediate containers in the batch, but in no case less than 12 immediate containers.

Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) If it is packaged with inert gases and the streptomycin or dihydrostreptomycin used has not been previously submitted; 5 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) In case of an initial request for the certification of a batch which is to be packaged in combination with a solvent which is not recognized by the U. S. P., or when any change is made in the composition of such solvent, five packages of the solvent included in the combination.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i) and (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of streptomycin for inhalation therapy and dihydrostreptomycin for inhalation therapy for veterinary use from certification.* Streptomycin for inhalation therapy and dihydrostreptomycin for inhalation therapy that conform to the requirements of paragraphs (a), (b), and (c) of this section shall be exempt from the requirements of section 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) They are intended solely for veterinary use and are conspicuously so labeled.

(2) The labels bear an expiration date that is not more than 48 months after the month during which the batch was last assayed and released by the manufacturer, except that such date is not more than 36 months if it is packaged with inert gases.

(3) The circular or other labeling within or attached to the package bears information that the antibiotics are for use only in the prevention or treatment of chronic respiratory disease (air-sac infection) in chickens and bears directions and warnings adequate for such use.

§ 146b.113 Dihydrostreptomycin-streptomycin sulfates.

(a) *Standards of identity, strength, quality, and purity.* Dihydrostreptomycin-streptomycin sulfates is a mixture of equal parts of dihydrostreptomycin sulfate and streptomycin sulfate. It is so purified and dried that:

(1) It is sterile.

(2) It is nontoxic.

(3) It is nonpyrogenic.

(4) It contains no histamine or histamine like substance.

(5) Its moisture content is not more than 5 percent.

(6) Its pH in an aqueous solution containing 0.1 gram of dihydrostreptomycin and 0.1 gram of streptomycin per milliliter is not less than 4.5 and not more than 7.0.

The dihydrostreptomycin sulfate used conforms to the standards prescribed by § 146b.103, except the standards for streptomycin content. The streptomycin sulfate used conforms to the standards prescribed by § 146b.101 (a).

(b) *Packaging.* It shall be packaged in accordance with the requirements prescribed by § 146b.101 (b), except that in case it is packaged for dispensing each immediate container shall contain not less than 0.5 gram of dihydrostreptomycin and 0.5 gram of streptomycin or multiples of each such salt up to and including 5.0 grams of dihydrostreptomycin and 5.0 grams of streptomycin.

(c) *Labeling.* It shall be labeled in accordance with the requirements prescribed by § 146b.101(c), except that each package shall bear on the outside wrapper or container and the immediate container the number of grams of dihydrostreptomycin, the number of grams of streptomycin, and the total number of grams of both salts in the immediate container. If it is intended for human parenteral use, its labeling shall also bear, as hereinafter indicated, the following:

(1) On the outside wrapper or container and on the immediate container, "Warning: For use only in the treatment of tuberculosis in patients who cannot tolerate full doses of streptomycin."

(2) On the circular or other labeling within or attached to the package, warnings to the effect that:

(i) Because of dihydrostreptomycin's potentiality for causing delayed deafness, this drug should be administered only to patients having tuberculosis that is amenable to treatment with dihydrostreptomycin or streptomycin but who cannot tolerate full doses of streptomycin.

(ii) Severe auditory impairment has been reported following a total parenteral dose of as little as 2 grams to 5 grams of dihydrostreptomycin. The auditory damage, which is usually permanent, may be delayed for a few weeks or up to several months.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch marks, and (unless they were previously submitted) the dates on which the latest assays of the dihydrostreptomycin and streptomycin used in making the batch were completed, the content of dihydrostreptomycin and streptomycin in each container, and the date on which the latest assay of the drug comprising such batch was completed. If such batch or any part thereof is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements described therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following made by him on an accurately representative sample of:

(i) The batch; content of dihydrostreptomycin and streptomycin, sterility, toxicity, pyrogens, histamine content, moisture, and pH.

(ii) The dihydrostreptomycin and streptomycin used in making the batch; potency, and if crystalline dihydrostreptomycin is used, crystallinity.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in the batch but in no case less than 6 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The dihydrostreptomycin used in making the batch; 3 packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146b.101 (b).

(iii) The streptomycin used in making the batch; three packages containing approximately 0.5 gram packaged in accordance with the requirements of § 146b.101 (b).

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility: 6 packages.

(ii) For sterility testing: 10 packages. Each such package shall contain not less than 0.5 gram of dihydrostreptomycin and 0.5 gram of streptomycin taken from different parts of such batch, and each shall be packaged in accordance with the requirements of § 146b.101 (b).

(5) No result referred to in subparagraph (2) of this paragraph, and no sample referred to in subparagraphs (3) (ii) and (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $10.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) and (4) (i) of this section; $4.00 for each sample submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and 4(ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146b.114 Streptomycin sulfate veterinary; dihydrostreptomycin sulfate veterinary; dihydrostreptomycin hydrochloride veterinary.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin sulfate veterinary is the sulfate salt of a kind of streptomycin or a mixture of two or more such salts. Dihydrostreptomycin sulfate veterinary and dihydrostreptomycin hydrochloride veterinary are the hydrogenated sulfate or hydrochloride salt of a kind of streptomycin or a mixture of two or more such salts. Each such drug may contain a suitable and harmless lubricant. Each such drug is so purified and dried that:

(1) Its potency is not less than 450 micrograms per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 14.0 percent.

(4) Its pH in aqueous solution of 0.2 gram per milliliter is not less than 3.0 and not more than 7.0.

(5) If it is dihydrostreptomycin sulfate veterinary or dihydrostreptomycin hydrochloride veterinary, its content of streptomycin is not more than 5 percent when calculated as streptomycin base.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container:

(1) The batch mark.

(2) The number of milligrams of streptomycin or dihydrostreptomycin per gram and the number of grams of the drug in the immediate container; and if the batch contains a lubricant, the name of such ingredient.

(3) The statement "Expiration date _____," the blank being filled in with the date which is 36 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 48 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(4) The statement "For use only in the manufacture of nonsterile veterinary drugs."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of milligrams of streptomycin or dihydrostreptomycin per gram, and the total number of grams of streptomycin or dihydrostreptomycin in each package. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, and streptomycin content if it is dihydrostreptomycin.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of 6 packages each containing approximately 1.0 gram taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations, other than the examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.115 Streptomycin sulfate powder oral veterinary; streptomycin sulfate granules oral veterinary; dihydrostreptomycin sulfate powder oral veterinary; dihydrostreptomycin sulfate granules oral veterinary; dihydrostreptomycin hydrochloride powder oral veterinary; dihydrostreptomycin hydrochloride granules oral veterinary.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin sulfate powder oral veterinary, streptomycin sulfate granules oral veterinary, dihydrostreptomycin sulfate powder oral veterinary, dihydrostreptomycin sulfate granules oral veterinary, dihydrostreptomycin hydrochloride powder oral veterinary, and dihydrostreptomycin hydrochloride granules oral veterinary are streptomycin sulfate veterinary, dihydrostreptomycin sulfate veterinary, or dihydrostreptomycin hydrochloride veterinary, with or without one or more suitable and harmless diluents and stabilizing agents and with or without one or more suitable sulfonamides. Its potency is not less than 3.75 grams per pound. Its moisture content is not more than 7.0 percent. The streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.114 (a). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. The composition of the immediate containers shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of streptomycin or dihydrostreptomycin per gram and the number of grams in the immediate container.

(iii) If it contains one or more sulfonamides, the name and quantity of each such ingredient.

(iv) The statement "Expiration date, ----------," the blank being filled in with the date that is 12 months (if its potency is less than 150 grams per pound) or 36 months (if its potency is 150 grams or more per pound) after the month during which the batch was certified, except that if the person who requests certification has submitted to the Commissioner results of tests and assays that show that such drug as prepared by him is stable for 24 months, 36 months, or 48 months, such date may be used for such drug.

(v) The statement "For oral veterinary use only."

(vi) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking," when packaged for repacking or for use as an ingredient in the manufacture of another drug, as the case may be.

(2) On the label and labeling, if it contains one or more sulfonamides, after the name "streptomycin sulfate powder oral veterinary," "streptomycin sulfate granules oral veterinary," "dihydrostreptomycin sulfate powder oral veterinary," "dihydrostreptomycin sulfate granules oral veterinary," "dihydrostreptomycin hydrochloride powder oral veterinary," or "dihydrostreptomycin hydrochloride granules oral veterinary," wherever such name appears, the words "with sulfonamide(s)," in juxtaposition with such name.

(3) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a bronchure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the streptomycin or dihydrostreptomycin used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each other ingredient used conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; potency, toxicity, moisture, pH, and streptomycin content if it is dihydrostreptomycin.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, unless each such container is packaged to contain more than 15 grams, in which case the sample shall consist of 15 grams for each 5,000 immediate containers in the batch, but in no case less than five 15-gram portions. Such samples shall be collected by taking single immediate containers or 15-gram portions at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; 6 packages containing approximately equal portions of not less than 1.0 gram each, packaged in accordance with the requirements of § 146b.114 (b).

(iii) In case of an initial request for certification, the other ingredients used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section; and

(2) If the Commissioner considers that investigations other than the exami-

nation of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) ***Exemption of streptomycin sulfate powder oral veterinary, streptomycin sulfate granules oral veterinary, dihydrostreptomycin sulfate powder oral veterinary, dihydrostreptomycin sulfate granules oral veterinary, dihydrostreptomycin hydrochloride powder oral veterinary, and dihydrostreptomycin hydrochloride granules oral veterinary from certification.*** Streptomycin sulfate powder oral veterinary, streptomycin sulfate granules oral veterinary, dihydrostreptomycin sulfate powder oral veterinary, dihydrostreptomycin sulfate granules oral veterinary, dihydrostreptomycin hydrochloride powder oral veterinary, and dihydrostreptomycin hydrochloride granules oral veterinary that conform to the requirements of paragraphs (a) (except that they may contain one or more essential vitamin and mineral substances for nutritive purposes), (b), and (c) of this section shall be exempt from the requirements of sections 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) The labels bear an expiration date that is not more than 48 months after the month during which the batch was last assayed and released by the manufacturer.

(2) If they contain added vitamins or minerals, the labels bear the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear a statement that solutions prepared with the drugs are stable for not more than 24 hours.

(4) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Bacterial enteritis in swine.

(ii) Bacterial calf scours.

(iii) Chronic respiratory disease (air-sac infection) in chickens.

(iv) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

§ 146b.116 Streptonicozid sulfate.

(a) *Standards of identity, strength, quality, and purity.* Streptonicozid sulfate is the crystalline sulfate compound of streptomycin and isonicotinic acid hydrazide. It is so purified and dried that:

(1) It contains not less than the equivalent of 583 micrograms of streptomycin per milligram and its isonicotinic acid hydrazide equivalent content is not less than 13.75 percent.

(2) It is sterile.

(3) It is nontoxic.

(4) It is nonpyrogenic.

(5) It contains no histamine nor histamine-like substance.

(6) Its moisture content is not more than 5 percent.

(7) Its pH in an aqueous solution containing the equivalent of 0.2 gram of streptomycin per milliliter is not less than 4.5 and not more than 7.5.

(8) Its absorptivity (1%, 1 cm.) is not less than 150 at 260 millimicrons.

The streptomycin used conforms to the requirements of § 146b.101 (a). The isonicotinic acid hydrazide used has a purity of not less than 98 percent and it has a melting point of not less than 169° C. and not more than 172° C.

(b) *Packaging.* It shall be packaged in accordance with the requirements of § 146b.101 (b), except that each immediate container shall contain the equivalent of not less than 1.0 gram of streptomycin.

(c) *Labeling.* In addition to the labeling requirements of § 146b.101(c)(1), each package shall bear on the outside wrapper or container and the immediate container the number of grams of equivalent streptomycin activity, the equivalent number of grams of isonicotinic acid hydrazide, and the number of grams of streptonicozid sulfate in the immediate container.

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of grams of streptomycin, isonicotinic acid hydrazide, and streptonicozid sulfate in each package and (unless it was previously submitted) the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, histamine content, moisture, pH, crystallinity, and absorptivity. If such batch or any part thereof is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) If such batch is packaged for dispensing, such person shall submit in connection with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than six immediate containers.

(ii) For sterility testing; 10 immediate containers.

Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(3) If such batch is packaged for repacking or for use in the manufacture of another drug, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; six packages, each containing the equivalent of approximately 1 gram of streptomycin activity.

(ii) For sterility testing; 10 packages, each containing the equivalent of approximately 0.5 gram of streptomycin activity.

Each such package shall be taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(4) In connection with contemplated requests for certification of repackaged batches or batches of another drug in the manufacture of which it is to be used, the manufacturer of the batch which is to be so repacked or used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (3) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted tests and results of assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $10.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i), (3) (i), and (4) of this section; $10.00 for all containers submitted in accordance with paragraph (d)(2)(ii) and 3(ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.117 Dihydrostreptomycin-streptomycin sulfates solution.

(a) *Standards of identity, strength, quality, and purity.* Dihydrostreptomycin-streptomycin sulfates solution is an aqueous solution of dihydrostreptomycin-streptomycin sulfates. Such solution conforms to all standards prescribed by § 146b.113(a) for dihydrostreptomycin-streptomycin sulfates, except the limitation on moisture content, and except that:

(1) Each milliliter shall contain not less than 200 milligrams each of dihydrostreptomycin and streptomycin and not more than 250 milligrams each of dihydrostreptomycin and streptomycin, unless it is intended solely for veterinary use and is conspicuously so labeled.

(2) It may contain suitable and harmless buffer substances, preservatives, and stabilizing agents. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(3) Its pH is not less than 5.0 and not more than 7.5.

(b) *Packaging.* It shall be packaged in accordance with the requirements of § 146b.106 (b).

(c) *Labeling.* It shall be labeled in accordance with the requirements of § 146b.106(c), except that:

(1) In lieu of the statement required on the outside wrapper or container and the immediate container by § 146b.106 (c) (1) (i) (*b*), if it is intended for human parenteral use it shall bear the statement "*Warning:* For use only in the treatment of tuberculosis in patients who cannot tolerate full doses of streptomycin."

(2) In lieu of the statements required by § 146b.106(c) (1) (iii) (*a*) and (*b*), the circular or other labeling within or attached to the package shall bear warnings to the effect that:

(i) Because of dihydrostreptomycin's potentiality for causing delayed deafness, this drug should be administered only to patients having tuberculosis that is amenable to treatment with dihydrostreptomycin or streptomycin but who cannot tolerate full doses of streptomycin.

(ii) Severe auditory impairment has been reported following total parenteral doses of as little as 2 grams to 5 grams of dihydrostreptomycin. The auditory damage, which is usually permanent, may be delayed for a few weeks or up to several months.

(d) *Request for certification; samples.* In addition to complying with the requirements of § 146b.113 (d), a person who requests certification of a batch shall submit in connection with his initial request one package containing approximately 5.0 grams of each other ingredient used in making the batch.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be the same as those prescribed by § 146b.113 (e), except that the fee for each immediate container in the sample of other ingredients required by paragraph (d) of this section shall be $4.00.

§ 146b.118 Streptomycin-penicillin-sulfonamide with kaolin and pectin; dihydrostreptomycin-penicillin-sulfonamide with kaolin and pectin.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-penicillin-sulfonamide with kaolin and pectin and dihydrostreptomycin-penicillin-sulfonamide with kaolin and pectin are dry mixtures of streptomycin sulfate or dihydrostreptomycin sulfate, crystalline penicillin G (sodium or potassium), one or more suitable sulfonamides, kaolin, and pectin, with or without bismuth subcarbonate and with or without one or more suitable and harmless preservatives, colorings, and flavorings. Its moisture content is not more than 2 percent. The pH of a suspension prepared as directed in its labeling is not less than 5.5 and not more than 7.5. The streptomycin used conforms to the standards prescribed by § 146b.101 (a), except § 146b.101 (a) (2), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103, except the standards for sterility, pyrogens, and histamine content. The crystalline penicillin G used conforms to the standards prescribed therefor by § 146a.24 (a) of this chapter, except § 146a.24 (a) (2) and (4). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall contain not less than 1.0 gram of streptomycin or dihydrostreptomycin and not less than 1,200,000 units of penicillin. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) On the immediate container, directions for preparing the suspension and the statement, "Suspension may be kept in refrigerator for 1 week without significant loss of potency."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch marks and (unless they were previously submitted) the dates on which the latest assays of the streptomycin or dihydrostreptomycin and penicillin used in making such batch were completed, the number of grams of streptomycin or dihydrostreptomycin and the number of units of penicillin in the immediate container, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; content of streptomycin or dihydrostreptomycin, content of penicillin, moisture, and pH.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin.

(iii) The penicillin used in making the batch; potency, toxicity, moisture, pH, crystallinity, heat stability, and penicillin G content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 6 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time the containers are being filled that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch; 5 packages, containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) The penicillin used in making the batch; 10 packages, containing approximately equal portions of not less than 60 milligrams each, packaged in accordance with the requirements of § 146a.24 (b).

(iv) In case of an initial request for certification, each other ingredient used in making the batch; one package of each, containing approximately 5.0 grams.

(4) No result referred to in subparagraph (2) (ii) and (iii) of this paragraph, and no sample referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.119 Streptomycin hydrochloride solution oral veterinary; streptomycin sulfate solution oral veterinary.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin hydrochloride solution oral veterinary and streptomycin sulfate solution oral veterinary are aqueous solutions of streptomycin hydrochloride or streptomycin sulfate, with one or more suitable and harmless preservatives. The drug may also contain one or more suitable and harmless buffer substances and stabilizing agents. Its potency is not less than 250 milligrams per milliliter. Its pH is not less than 5.0 and not more than 8.0. It is nontoxic. Each preservative, buffer substance, and stabilizing agent used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on the outside wrapper or container and the immediate container:

(1) The batch mark.

(2) The number of milligrams of streptomycin in each milliliter of the immediate container.

(3) The statement "Expiration date ------," the blank being filled in with the date which is 12 months after the month during which the batch was certified.

(4) The name and quantity of each preservative used.

(5) The statement "For oral veterinary use only."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and the number of milligrams of streptomycin per milliliter. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, and pH.

(2) Such person shall also submit with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers.

(ii) In case of an initial request for certification, each other ingredient used in making the batch; 1 package of each containing approximately 5 grams.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of streptomycin hydrochloride solution oral veterinary and streptomycin sulfate solution oral veterinary from certification.* Streptomycin hydrochloride solution oral veterinary and streptomycin sulfate solution oral veterinary that conform to the requirements of paragraphs (a) (except that they may contain one or more essential vitamin and mineral substances for nutritive purposes), (b), and (c) of this section shall be exempt from the requirements of sections 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) The labels bear an expiration date that is not more than 12 months after the month during which the batch was last assayed and released by the manufacturer.

(2) If they contain added vitamins or minerals, the labels bear the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear a statement that solutions prepared with the drugs are stable for not more than 24 hours.

(4) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Bacterial enteritis in swine.

(ii) Bacterial calf scours.

(iii) Chronic respiratory disease (air-sac infection) in chickens.

(iv) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

§ 146b.120 Dihydrostreptomycin-streptomycin sulfates with isonicotinic acid hydrazide.

Dihydrostreptomycin-streptomycin sulfates with isonicotinic acid hydrazide conforms to all requirements and is subject to all procedures prescribed by § 146b.113 for dihydrostreptomycin-streptomycin sulfates, except that:

(a) It contains not less than 100 milligrams of isonicotinic acid hydrazide for each 0.5 gram of dihydrostreptomycin-streptomycin sulfates. The isonicotinic acid hydrazide used has a purity of not less than 98 percent and has a melting point of not less than 169° C. and not more than 172° C.

(b) In addition to the labeling prescribed by § 146b.113(c), each package shall bear on the outside wrapper or container and the immediate container the number of grams of isonicotinic acid hydrazide in the immediate container, and its expiration date shall be 18 months after the month during which the batch was certified.

(c) In addition to complying with the requirements of § 146b.113 (d), a person who requests certification of a batch shall submit with his request a statement showing the number of grams of isonicotinic acid hydrazide in each package, and in case of an initial request for certification, a sample consisting of approximately 5.0 grams of the isonicotinic acid hydrazide used in making the batch.

(d) The fee for the services rendered with respect to the sample of isonicotinic acid hydrazide submitted in accordance with the requirements prescribed therefor by this section shall be $4.00.

§ 146b.121 Streptomycin-erythromycin ointment.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-erythromycin ointment is streptomycin and erythromycin in a suitable and harmless ointment base, with or without one or more suitable sulfonamides and with or without suitable and harmless dispersing and suspending agents. Its moisture content is not more than 1.0 percent. It contains per gram not less than 3 milligrams of streptomycin and not less than 5 milligrams of erythromycin. The streptomycin used conforms to the requirements of § 146b.101(a), except § 146b.101(a) (2), (3), (4), and (5). The erythromycin used is produced by the growth of *Streptomyces erythreus*, has a potency of not less than 850 micrograms per milligram (on the anhydrous basis), has a moisture content of not more than 10 percent, its pH in a saturated aqueous solution is not less than 8 and not more than 10.5, and it gives a characteristic color test with acetone and hydrochloric acid. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Streptomycin-erythromycin ointment shall be packaged in collapsible tubes which shall be well-closed containers as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of streptomycin and the number of milligrams of erythromycin in each gram or milliliter of the batch.

(iii) If it contains one or more sulfonamides, the name and quantity of each such ingredient in each gram or milliliter of the batch.

(iv) The statement "For veterinary use only."

(v) The statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified except that the blank may be filled in with the date which is 18 months, 24 months, or 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assay showing that after having been stored for such period of time, such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section: *Provided, however,* That such expiration date may be omitted from the immediate container if it contains a single dose and it is packaged in an individual wrapper or container.

(2) On the label and labeling, if it contains one or more sulfonamides, after the name "streptomycin-erythromycin ointment," wherever it appears, the words "with sulfonamide(s)," in juxtaposition with such name.

(3) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the dates on which the latest assays of the streptomycin and erythromycin used in making such batch were completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The streptomycin and erythromycin used in making the batch: Potency, pH, moisture, and color-identity test, if it is erythromycin.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 6 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin used in making the batch: 6 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) The erythromycin used in making the batch: 5 packages, each containing approximately equal portions of not less than 0.5 gram.

(iv) In case of an initial request for certification, the ingredients used in making the ointment base of the batch: 1 package of each, containing approximately 200 grams, except for the suspending or dispersing agents and sulfonamides used, in which case the sample shall consist of approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no samples referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such result or samples have been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.122 Streptomycin - chlortetracycline - chloramphenicol-bacitracin dental cement; dihydrostreptomycin-chlortetracycline - chloramphenicol-bacitracin dental cement.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-chlortetracycline-chlorampenicol - bacitracin dental cement and dihydrostreptomycin-chlortetracycline - chloramphenicol-bacitracin dental cement are streptomycin or dihydrostreptomycin, chlortetracycline, chloramphenicol, and bacitracin in a base composed of suitable and harmless inert inorganic salts and oxides. Its moisture content is not more than 1 percent. It contains not less than 1.0 milligram of streptomycin or dihydrostreptomycin, not less than 1.0 milligram of chlortetracycline, not less than 1.0 milligram of chloramphenicol, and not less than 50 units of bacitracin per gram. The streptomycin used conforms to the standards prescribed by § 146b.101 (a), except § 146b.101 (a) (2), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103, except the standards for sterility, pyrogens, and histamine. The chlortetracycline used conforms to the standards prescribed by § 146c.201 (a) of this chapter, except § 146c.201 (a) (2), (4), and (5). The chloramphenicol used conforms to the standards prescribed by § 146d.301 (a) of this chapter, except § 146d.301 (a) (2), (4), and (5). The bacitracin used conforms to the standards prescribed by § 146e.401 (a) of this chapter, except § 146e.401 (a) (2) and (4). Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Each batch of dental cement shall be packaged in immediate containers of transparent glass that meet the test for tight containers as defined by the U. S. P., and so sealed that the contents cannot be used without destroying such seal. The immediate container and closure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106 (b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates of the latest tests and assays of the streptomycin or dihydrostreptomycin, chlortetracycline, chloramphenicol, and bacitracin used in making the batch.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: Potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(iii) The chlortetracycline used in making the batch: Potency, toxicity, moisture, and pH.

(iv) The chloramphenicol used in making the batch: Potency, toxicity, pH,

specific rotation, melting point, and extinction coefficient.

(v) The bacitracin used in making the batch: Potency, toxicity, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 package for each 5,000 packages in the batch, but in no case less than 7 packages.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: 6 packages containing approximately equal portions of not less than 0.5 gram.

(iii) The chlortetracycline used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams.

(iv) The chloramphenicol used in making the batch: 10 packages, each containing approximately equal portions of not less than 300 milligrams.

(v) The bacitracin used in making the batch: 6 packages, each containing approximately equal portions of not less than 0.5 gram.

(vi) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii), (iii), (iv), and (v) of this paragraph, and no sample referred to in subparagraph (3) (ii), (iii), (iv), and (v) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), (v), and (vi) of this section; $60.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.123 Streptomycin-sodium sulfathiazole solution veterinary; dihydrostreptomycin-sodium sulfathiazole solution veterinary.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-sodium sulfathiazole solution veterinary and dihydrostreptomycin-sodium sulfathiazole solution veterinary are streptomycin or dihydrostreptomycin and sodium sulfathiazole dissolved in a suitable and harmless vehicle. Each milliliter contains not less than 35 milligrams of streptomycin or dihydrostreptomycin and not less than 25 milligrams of sodium sulfathiazole. It is sterile. It is nontoxic. It is nonpyrogenic. It contains no histamine nor histamine-like substance. Its pH is not less than 5.0 and not more than 8.0. The streptomycin used conforms to the standards prescribed therefor by § 146b.101(a), except subparagraph (6). The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103, except the standard for moisture. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling.* It shall be packaged and labeled in accordance with the requirements of § 146b.106 (b) and (c), except that in addition to the requirements of paragraph (c) each package shall bear on the outside wrapper or container and the immediate container:

(1) The composition of the vehicle.

(2) The number of milligrams of sodium sulfathiazole in each milliliter of the batch.

(3) The statement "For veterinary use only."

(c) *Requests for certification, samples; fees.* The person who requests certification of a batch shall submit in connection with his request the same information and number of samples for the batch as prescribed by § 146b.106 (d), and the fee for the services rendered with respect to each such batch shall be the same as that prescribed by § 146b.106 (e).

§ 146b.124 Streptomycin-polymyxin-neomycin ointment; dihydrostreptomycin-polymyxin-neomycin ointment.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-polymyxin-neomycin ointment and dihydrostreptomycin-polymyxin-neomycin ointment are streptomycin or dihydrostreptomycin, polymyxin, and neomycin in a suitable and harmless ointment base, with or without one or more suitable sulfonamides, and with or without suitable and harmless dispersing and suspending agents. Their moisture content is not more than 1 percent. Their potency is such that when used as directed in their labeling each dose shall contain not less than 250 milligrams of streptomycin or dihydrostreptomycin, 100,000 units of polymyxin B, and 150 milligrams of neomycin. The streptomycin used conforms to the requirements of § 146b.101 (a), except § 146b.101 (a) (2), (3), (4), and (5). The dihydrostreptomycin used conforms to the requirements of § 146b.103, except the standards for sterility, toxicity, pyrogens, and histamine. The polymyxin B used conforms to the requirements prescribed for polymyxin B by § 146b.107 (a), except the standard for toxicity. The neomycin used conforms to the requirements prescribed for neomycin by § 146e.410 (a) (2) of this chapter, except the standard for toxicity. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Each batch of ointment shall be packaged in collapsible tubes which shall be well-closed containers as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of streptomycin or dihydrostreptomycin, the number of milligrams of neomycin, and the number of units of polymyxin B in each gram of the batch.

(iii) If the batch contains one or more sulfonamides, the name and quantity of each such ingredient per gram of the batch.

(iv) The statement "For veterinary use only."

(v) The statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified: *Provided, however,* That such expiration date may be omitted from the immediate container if it contains a single dose and it is packaged in an individual wrapper or container.

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the dates on which the latest assays of the streptomycin or dihydrostreptomycin, polymyxin B, in neomycin used in making such batch were completed; the quantity of each such ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: Potency, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(iii) The polymyxin B used in making the batch: Potency.

(iv) The neomycin used in making the batch: Potency, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 7 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: 6 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) The polymyxin B used in making the batch: 5 packages containing approximately equal portions of not less than 0.5 gram each.

(v) In case of an initial request for certification, the ingredients used in making the batch: 1 package of each ointment-base ingredient, containing approximately 200 grams; 1 package of each suspending or dispersing agent used, containing approximately 5 grams; 1 package of each sulfonamide used, containing approximately 5 grams.

(4) The results referred to in subparagraph (2) (ii), (iii), and (iv) of this paragraph and the samples referred to in subparagraph (3) (ii), (iii), and (iv) of this paragraph are not required if such results or samples have been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), and (v) of this section; $6.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigation.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.125 Streptomycin-dihydrostreptomycin for inhalation therapy.

(a) Streptomycin-dihydrostreptomycin for inhalation therapy conforms to all requirements and is subject to all procedures prescribed by § 146b.112 for streptomycin for inhalation therapy and dihydrostreptomycin for inhalation therapy, except that it is a mixture of equal parts of streptomycin and dihydrostreptomycin.

(b) *Exemption of streptomycin-dihydrostreptomycin for inhalation therapy from certification.* Streptomycin-dihydrostreptomycin for inhalation therapy that conforms to the requirements of paragraph (a) of this section shall be exempt from the requirements of sections 502 (1) and 507 of the act if it complies with all the following conditions:

(1) It is intended solely for veterinary use and is conspicuously so labeled.

(2) The label bears an expiration date that is not more than 48 months after the month during which the batch was last assayed and released by the manufacturer.

(3) The circular or other labeling within or attached to the package bears information that the antibiotics are for use only in the prevention or treatment of chronic respiratory disease (air-sac infection) in chickens and bears directions and warnings adequate for such use.

§ 146b.126 Streptomycin-neomycin powder; dihydrostreptomycin-neomycin powder.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin-neomycin powder and dihydrostreptomycin-neomycin powder are streptomycin and neomycin or dihydrostreptomycin and neomycin, with or without suitable and harmless absorbent ingredients, buffer substances, preservatives, diluents, colorings, and flavorings. It contains not less than 15 milligrams of streptomycin or dihydrostreptomycin and not less than 5.25 milligrams of neomycin per gram of powder. Its moisture content is not more than 7.5 percent. The streptomycin used conforms to the standards prescribed therefor by § 146b.101(a), except § 146b.101(a) (2), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103, except the standards for sterility, pyrogens, and histamine content. The neomycin used conforms to the standards prescribed therefor by § 146e.410(a)(2) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months or 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates on which the latest assays of the streptomycin or dihydrostreptomycin and neomycin used in making the batch were completed, the number of milligrams of streptomycin or dihydrostreptomycin and the number of milligrams of neomycin in each gram of the batch, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request, results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: The number of milligrams of streptomycin or dihydrostreptomycin and the number of milligrams of neomycin per gram, and moisture content.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: Potency, toxicity, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin.

(iii) The neomycin used in making the batch: Potency, toxicity, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: 5 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) The neomycin used in making the batch: 5 packages containing approximately equal portions of not less than 0.5 gram each.

(iv) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) and (iii) of this paragraph, and no sample referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) of this section.

(2) If the Commissioner considers that investigations other than examinations of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.127 Streptomycin solution for inhalation therapy veterinary; dihydrostreptomycin solution for inhalation therapy veterinary.

(a) *Standards of identity, strength, quality, and purity.* Streptomycin solution for inhalation therapy veterinary and dihydrostreptomycin solution for inhalation therapy veterinary is a suitable and harmless aqueous-organic solution of streptomycin or dihydrostreptomycin, with or without suitable and harmless preservatives, colorings, volatile oils, flavorings, buffer substances, and stabilizing agents. Its potency is not less than 50 milligrams per milliliter. Its pH is not less than 5.0 and not more than 8.0. The streptomycin or dihydrostreptomycin used conforms to the standards prescribed by § 146b.101 (a) or § 146b.103(a), except the standards for sterility, pyrogens, and histamine, or to the standards prescribed by § 146b.114(a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of streptomycin or dihydrostreptomycin in each milliliter of the batch.

(iii) The statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(iv) The name and quantity of each preservative used.

(v) The statement "For veterinary use only."

(2) On a circular or other labeling within or attached to the package directions and warnings adequate for the use of the drug in the treatment of chronic respiratory disease (air-sac infection) in poultry.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch and the number of milligrams of streptomycin or dihydrostreptomycin per milliliter in the batch. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency and pH.

(2) Such person shall also submit with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers.

(ii) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each containing approximately 5 grams.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146b.128 Streptomycin-polymyxin in gel; dihydrostreptomycin-polymyxin in gel.

Streptomycin-polymyxin in gel and dihydrostreptomycin-polymyxin in gel conform to all requirements and are subject to all procedures prescribed by § 146b.108 for streptomycin in gel and dihydrostreptomycin in gel, except that:

(a) Each milliliter contains not less than 4,000 units of polymyxin. The polymyxin used conforms to the standards prescribed therefor by § 146b.107 (a).

(b) Its pH is not less than 5.5 and not more than 7.0.

(c) In lieu of the labeling prescribed by § 146b.108(c) (1) (i), the expiration date shall be 18 months.

(d) In addition to complying with the requirements of § 146b.108 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the polymyxin used in making the batch for potency and toxicity. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the streptomycin-polymyxin in gel or dihydrostreptomycin-polymyxin in gel and (unless previously submitted) a sample consisting of 5 packages, each containing approximately equal portions of not less than 0.5 gram of the polymyxin used in making the batch.

(e) The fee for the services rendered with respect to each immediate container of the sample of streptomycin-polymyxin in gel or dihydrostreptomycin-polymyxin in gel submitted in accordance with the requirements of this section shall be $6.00. The fee for each container of polymyxin shall be $4.00.

§ 146b.129 Streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary.

(a) *Standards of identity, strength, quality, and purity; packaging; labeling; request for certification (samples); fees.* Streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary conforms to all requirements and is subject to all procedures prescribed by § 146b.115 for streptomycin sulfate powder oral veterinary and dihydrostreptomycin sulfate powder oral veterinary, except that it is a mixture of equal parts of streptomycin sulfate veterinary and dihydrostreptomycin sulfate veterinary.

(b) *Exemption of streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary from certification.* Streptomycin sulfate-dihydrostreptomycin sulfate powder oral veterinary that conforms to the requirements of paragraph (a) of this section (except that it may contain one or more essential vitamin and mineral substances for nutritive purposes) shall be exempt from the requirements of sections 502 (l) and 507 of the act, if it complies with all the following conditions:

(1) The labels bear an expiration date that is not more than 48 months after the month during which the batch was last assayed and released by the manufacturer.

(2) If it contains added vitamins or minerals, the labels bear the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear a statement that solutions prepared with the drug are stable for not more than 24 hours.

(4) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Bacterial enteritis in swine.

(ii) Bacterial calf scours.

(iii) Chronic respiratory disease (air-sac infection) in chickens.

(iv) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

§ 146b.130 Streptomycin and para-aminobenzoic acid powder for inhalation therapy; dihydrostreptomycin and para-aminobenzoic acid powder for inhalation therapy.

Streptomycin and para-aminobenzoic acid powder for inhalation therapy and dihydrostreptomycin and para-aminobenzoic acid powder for inhalation therapy conform to all requirements and are subject to all procedures prescribed by § 146b.112 (a), (b), and (c) for streptomycin for inhalation therapy veterinary and dihydrostreptomycin for inhalation therapy veterinary, except that:

(a) They contain para-aminobenzoic acid.

(b) In addition to the labeling prescribed by § 146b.112 (c), each package shall bear on its label and labeling the number of milligrams of para-aminobenzoic acid in each immediate container and the statements: "For veterinary use only," and "Caution: Discontinue use 24 hours before birds are slaughtered for human consumption." The expiration date shall be 12 months after the month during which the batch was certified.

(c) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the streptomycin or dihydrostreptomycin used in making such batch was completed, the potency per gram of powder, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per gram of powder and average moisture.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: Potency, toxicity moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One immediate container for each 5,000 containers in the batch, but in no case less than five such containers. Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time the containers are being filled that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: Five packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5.0 grams.

(4) The results referred to in subparagraph (2) (ii) of this paragraph and the samples referred to in subparagraph (3) (ii) of this paragraph are not required if such results or samples have been previously submitted.

(d) *Fees.* The fees for the service rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (c) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter, for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

146b.131 Streptomycin-polymyxin tablets; dihydrostreptomycin-polymyxin tablets.

Streptomycin-polymyxin tablets and dihydrostreptomycin-polymyxin tablets are tablets that conform to all requirements and are subject to all procedures prescribed by § 146b.104 for streptomycin tablets and dihydrostreptomycin tablets, except that:

(a) Each tablet contains not less than 25,000 units of polymyxin. The polymyxin used conforms to the standards prescribed therefor by § 146b.107(a).

(b) Each package shall bear on its outside wrapper or container and the immediate container the number of units of polymyxin in each tablet of the batch.

(c) The expiration date shall appear on the immediate container.

(d) In addition to complying with the requirements of § 146b.104(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of polymyxin used in making the batch for potency and toxicity. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages each containing approximately equal portions of not less than 0.5 gram of the polymyxin used in making the batch.

(e) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (d) of this section shall be:

(1) $1.00 for each tablet.

(2) $4.00 for each immediate container of polymyxin.

§ 146b.132 Streptomycin-neomycin for inhalation therapy veterinary; dihydrostreptomycin-neomycin for inhalation therapy veterinary.

(a) *Identity; packaging; labeling.* Streptomycin-neomycin for inhalation therapy veterinary and dihydrostreptomycin-neomycin for inhalation therapy veterinary conform to all requirements and are subject to all procedures prescribed by § 146b.112 (a), (b), and (c), except that:

(1) For each 5 grams of streptomycin or dihydrostreptomycin, it contains 1 gram of neomycin. The neomycin used conforms to the standards prescribed therefor by § 146e.410(a) of this chapter.

(2) In addition to the labeling prescribed by § 146b.112(c), each package shall bear on its label and labeling the number of grams of neomycin in each immediate container and the statements "For veterinary use only" and "Caution: Do not use on laying hens." The expiration date of the drug shall be 18 months.

(b) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates on which the latest assays of the streptomycin or dihydrostreptomycin and neomycin used in making the batch were completed, the number of grams of streptomycin or dihydrostreptomycin and the number of grams of neomycin in the batch, the quantity of each other ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: The number of grams of streptomycin or dihydrostreptomycin and the number of grams of neomycin per container, and moisture content.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: Potency, toxicity, pH, streptomycin content if it is dihydrostreptomycin, and

crystallinity if it is crystalline dihydrostreptomycin.

(iii) The neomycin used in making the batch: Potency, toxicity, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One immediate container for each 5,000 immediate containers in the batch; but in no case less than five immediate containers, collected by taking single immediate containers throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The streptomycin or dihydrostreptomycin used in making the batch: Five packages containing equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101(b).

(iii) The neomycin used in making the batch: Five packages containing approximately equal portions of not less than 0.5 gram each.

(iv) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) The results referred to in subparagraph (2) (ii) and (iii) of this paragraph and the samples referred to in subparagraph (3) (ii) and (iii) of this paragraph are not required if such results or samples have been previously submitted.

(c) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container submitted in accordance with paragraph (b)(3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container submitted in accordance with paragraph (b)(3)(i) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146b.133 Dihydrostreptomycin-neomycin-polymyxin aerosol solution veterinary.

(a) *Standards of identity, strength, quality, and purity.* Dihydrostreptomycin-neomycin-polymyxin aerosol solution veterinary is an aqueous solution of dihydrostreptomycin, neomycin, and polymyxin with or without one or more suitable and harmless preservatives and with one or more suitable gas propellants. Its potency is such that when it is used as directed in its labeling each dose shall contain 250 milligrams of dihydrostreptomycin, 100 milligrams of neomycin, and 71,000 units of polymyxin B. Its pH is not less than 4.0 nor more than 6.0. The dihydrostreptomycin used conforms to the requirements of § 146b.103, except the standards for sterility, toxicity, pyrogens, and histamine. The neomycin used conforms to the requirements prescribed for neomycin by § 146e.410(a)(2) of this chapter, except the standard for toxicity. The polymyxin B used conforms to the requirements prescribed for polymyxin B by § 146b.107(a), except the standard for toxicity. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain a sufficient quantity of propellant to permit the ejection of the volume of drug indicated, whether administered in either single or multiple doses.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of dihydrostreptomycin, the number of milligrams of neomycin, and the number of units of polymyxin B in each milliliter of the batch, or in each prescribed dose.

(iii) The name and quantity of each preservative used in making the batch and the name of each propellant.

(iv) The statement "For udder instillation of cattle only."

(v) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(vi) The warning required by § 146.14 of this chapter.

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the dates on which the latest assays of the dihydrostreptomycin, polymyxin B, and neomycin used in making such batch were completed; the quantity of each such ingredient used in making the batch; the date on which the latest assay of the drug comprising such batch was completed; and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and pH.

(ii) The dihydrostreptomycin used in making the batch: Potency, pH, moisture, streptomycin content, and crystallinity if it is crystalline dihydrostreptomycin sulfate.

(iii) The polymyxin B used in making the batch: Potency.

(iv) The neomycin used in making the batch: Potency, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 7 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The dihydrostreptomycin used in making the batch: 6 packages containing approximately equal portions of not less than 0.5 gram each, packaged in accordance with the requirements of § 146b.101(b).

(iii) The polymyxin B used in making the batch: 5 packages containing approximately equal portions of not less than 0.5 gram each.

(iv) The neomycin used in making the batch: 5 packages containing approximately equal portions of not less than 0.5 gram each.

(v) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each containing approximately 5 grams.

(4) The results referred to in subparagraph (2) (ii), (iii), and (iv) of this paragraph and the samples referred to in subparagraph (3) (ii), (iii), and (iv) of this paragraph are not required if such results or samples have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d)(3) (ii), (iii), (iv), and (v) of this section; $6.00 for each immediate container submitted in accordance with paragraph (d)(3)(i) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigation.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

PART 146c—CERTIFICATION OF CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE- (OR TETRACYCLINE-) CONTAINING DRUGS

Sec.

146c.201 Chlortetracycline hydrochloride. (chlortetracycline hydrochloride salt).

146c.202 Chlortetracycline hydrochloride ointment; chlortetracycline calcium ointment; chlortetracycline calcium cream; tetracycline hydrochloride ointment (tetracycline hydrochloride in oil suspension); tetracycline ointment (tetracycline cream).

146c.203 Chlortetracycline troches (chlortetracycline hydrochloride troches); tetracycline hydrochloride troches.

146c.204 Chlortetracycline hydrochloride capsules; tetracycline hydrochloride capsules; tetracycline capsules; tetracycline phosphate complex capsules.

146c.205 Chlortetracycline powder (chlortetracycline hydrochloride powder); tetracycline hydrochloride powder; tetracycline powder.

146c.206 Chlortetracycline ophthalmic (chlortetracycline hydrochloride ophthalmic); tetracycline hydrochloride ophthalmic.

146c.207 Chlortetracycline hydrochloride tablets; tetracycline hydrochloride tablets; tetracycline tablets.

146c.208 Chlortetracycline otic (chlortetracycline hydrochloride otic, chlortetracycline hydrochloride for ear solution); tetracycline hydrochloride otic (tetracycline hydrochloride for ear solution).

146c.209 Chlortetracycline dental cones (chlortetracycline hydrochloride dental cones).

146c.210 Chlortetracycline dental paste (chlortetracycline hydrochloride dental paste).

146c.211 Chlortetracycline surgical powder (chlortetracycline hydrochloride surgical powder); tetracycline hydrochloride surgical powder.

146c.212 Chlortetracycline suppositories (chlortetracycline hydrochloride suppositories); tetracycline hydrochloride suppositories.

146c.213 Chlortetracycline gauze packing (chlortetracycline hydrochloride gauze packing).

146c.214 Chlortetracycline dressing (chlortetracycline hydrochloride dressing).

146c.215 Chlortetracycline with vasoconstrictor (chlortetracycline hydrochloride with vasoconstrictor); chlortetracycline with_____ (chlortetracycline hydrochloride with _____) (the blank being filled in with the common or usual name of the vasoconstrictor).

146c.216 Tetracycline hydrochloride-oleandomycin ointment.

146c.217 Chlortetracycline calcium syrup (chlortetracycline calcium oral drops); tetracycline syrup (tetracycline oral drops); tetracycline magnesium syrup (tetracycline magnesium oral drops).

146c.218 Tetracycline hydrochloride.

146c.219 Crude chlortetracycline oral veterinary.

146c.220 Tetracycline.

146c.221 Tetracycline hydrochloride for intramuscular use; tetracycline phosphate complex for intramuscular use.

146c.222 Tetracycline hydrochloride oral suspension (tetracycline hydrochloride homogenized mixture); tetracycline phosphate complex oral suspension (tetracycline phosphate complex oral drops); tetracycline hydrochloride oral solution; tetracycline calcium oral suspension; tetracycline oral suspension.

146c.223 Chlortetracycline-neomycin-streptomycin-penicillin ointment; chlortetracycline-neomycin-dihydrostreptomycin-penicillin ointment; tetracycline hydrochloride-neomycin-streptomycin-penicillin ointment; tetracycline hydrochloride-neomycin dihydrostreptomycin-penicillin ointment.

146c.224 Tetracycline hydrochloride-nystatin capsules; tetracycline phosphate complex-nystatin capsules.

146c.225 Tetracycline hydrochloride-nystatin tablets.

146c.226 Tetracycline and vasoconstrictor suspension; tetracycline and ___ (the blank being filled in with the common or usual name of the vasoconstrictor) suspension.

146c.227 Chlortetracycline spray dressing (chlortetracycline hydrochloride spray dressing).

146c.228 Tetracycline hydrochloride-neomycin tablets.

146c.229 Tetracycline-nystatin oral suspension; tetracycline phosphate complex-nystatin oral suspension (tetracycline phosphate complex-nystatin oral drops).

146c.230 Chlortetracycline hydrochloride powder topical; tetracycline hydrochloride powder topical.

146c.231 Capsules tetracycline and oleandomycin phosphate; capsules tetracycline and triacetyloleandomycin; capsules tetracycline hydrochloride and oleandomycin phosphate; capsules tetracycline hydrochloride and triacetyloleandomycin.

146c.232 Tetracycline phosphate complex.

146c.233 Tetracycline-oleandomycin phosphate for oral suspension.

146c.234 Capsules tetracycline hydrochloride and novobiocin; capsules tetracycline phosphate complex and novobiocin.

146c.235 Tetracycline hydrochloride-oleandomycin phosphate for aqueous injection.

146c.236 Tetracycline-nystatin for oral suspension.

146c.237 Chlortetracycline-neomycin-streptomycin ointment; chlortetracycline-neomycin-dihydrostreptomycin ointment; tetracycline hydrochloride-neomycin-streptomycin ointment; tetracycline hydrochloride-neomycin-dihydrostreptomycin ointment.

146c.238 Tablets tetracycline hydrochloride and novobiocin.

146c.239 Tetracycline-novobiocin for oral suspension.

146c.240 Tetracycline-triacetyloleandomycin syrup (tetracycline-triacetyloleandomycin oral drops; tetracycline – triacetyl – oleandomycin homogenized mixture).

146c.241 Chlortetracycline seed.

146c.242 Tetracycline—neomycin complex powder topical; tetracycline hydrochloride-neomycin sulfate powder topical.

146c.243 Capsules tetracycline hydrochloride - triacetyloleandomycinnystatin.

146c.244 Tetracycline hydrochloride-neomycin spray ointment topical.

146c.245 Tetracycline-triacetyloleandomycin for oral suspension.

146c.246 Tetracycline hydrochloride-neomycin in oil suspension.

146c.247 Chlortetracycline hydrochloride impregnated surgical silk.

146c.248 Rolitetracycline.

146c.249 Rolitetracycline for intravenous use.

146c.250 Rolitetracycline for intramuscular use.

146c.251 Demethylchlortetracycline hydrochloride.

146c.252 Capsules demethylchlortetracycline hydrochloride.

146c.253 Demethylchlortetracycline.

146c.254 Demethylchlortetracycline for oral suspension.

146c.255 Demethylchlortetracycline syrup (demethylchlortetracycline oral drops).

146c.256 Chlortetracycline hydrochloride in oil oral veterinary.

146c.257 Tetracycline-amphotericin B for oral syrup; tetracycline-amphotericin B for oral drops.

146c.258 Demethylchlortetracycline hydrochloride ointment.

146c.259 Demethylchlortetracycline hydrochloridenystatin capsules.

146c.260 Capsules tetracycline phosphate complex amphotericin B.

146c.261 Tetracycline-novobiocin oral suspension (tetracycline-novobiocin oral drops; tetracycline-novobiocin syrup).

146c.262 Tetracycline-amphotericin B syrup; tetracycline-amphotericin B oral drops.

146c.263 Demethylchlortetracycline - nystatin for oral suspension.

AUTHORITY: §§ 146c.201 to 146c.263 issued under sec. 507, 59 Stat. 463 as amended; 21 U.S.C. 357.

§ 146c.201 Chlortetracycline hydrochloride (chlortetracycline hydrochloride salt).

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline hydrochloride is the yellow hydrochloride salt or crystalline hydrochloride salt of a kind of chlortetracycline or a mixture of two or more such salts with or without one or more suitable and harmless buffer substances if it is intended for intravenous use. It is so purified and dried that:

(1) Its potency, and the potency of the chlortetracycline used in the manufacture of chlortetracycline for intravenous use, is not less than 900 micrograms per milligram, except if it is intended for use solely in the manufacture of a veterinary drug for nonparenteral use its potency is not less than 820 micrograms per milligram;

(2) It is sterile;

(3) It is nontoxic;

(4) It is nonpyrogenic;

(5) It contains no histamine nor histamine-like substances;

(6) Its moisture content is not more than 2.0 percent;

(7) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2.3 and not more than 3.3, except if it is intended for intravenous use and it contains buffer substances its pH is not less than 8 and not more than 9.5.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents can-

not be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is intended for intravenous use, it shall be packaged in immediate containers of colorless, transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness; each such container shall contain not more than 1.0 gram unless it is intended solely for veterinary use and is conspicuously so labeled, and each shall contain one or more suitable and harmless buffer substances, or each shall be packaged in combination with a container of a suitable and harmless diluent.

(c) *Labeling*—(1) *It is packaged for dispensing and it is intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____;" the blank being filled in with the date that is 12 months, or if it is crystalline chlortetracycline 60 months, after the month during which the batch was certified, except that if it is crystalline chlortetracycline and it contains buffer substances the blank shall be filled in with the date that is 36 months after the month during which the batch was certified.

(ii) On the circular or other labeling within or attached to the package, a statement of the conditions under which such solutions should be stored, including a reference to their instability when stored under other conditions, and a statement, "Sterile solutions must be injected immediately after preparation."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except, if it is not intended for intravenous use, in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity. If it is intended for intravenous use, the labeling shall conform with the requirements prescribed by § 1.106(c) of this chapter and to the requirements of subparagraph (1) (i) and (ii) of this paragraph.

(3) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The potency per milligram and the number of grams in the immediate container.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The information required by subparagraph (1) (i) of this paragraph.

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of milligrams in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed; and if it is intended for intravenous use and contains buffer substances, the date and the results of the latest test for potency of the chlortetracycline used in making such batch. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, histamine content, crystallinity (if it is the crystalline salt), moisture, and pH. If such batch or any part thereof is to be packaged with a solvent such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) If such batch is packaged for dispensing, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 1 immediate container for each 5,000 immediate containers in such batch, but in no case less than 8 immediate containers.

(ii) For sterility testing; 10 immediate containers.

Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(3) If such batch is packaged for repacking or for use as an ingredient in the manufacture of another drug, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 5 packages, each containing approximately 0.5 gram.

(ii) For sterility testing; 10 packages, each containing approximately 40 milligrams.

Each such package shall be packaged in accordance with the requirements of paragraph (b) of this section.

(4) In connection with contemplated requests for certification of repacked batches or batches of another drug in the manufacture of which it is to be used, the manufacturer of a batch which is to be so repacked or used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (3) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(5) If such batch is intended for intravenous use and it contains buffer substances, such person shall submit in connection with his request (unless it has been previously submitted) one immediate container containing approximately 0.5 gram of the chlortetracycline used in making such batch.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $10.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i), (3) (i), and (4) of this section; $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (5) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) and (3) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.202 Chlortetracycline hydrochloride ointment; chlortetracycline calcium ointment; chlortetracycline calcium cream; tetracycline hydrochloride ointment (tetracycline hydrochloride in oil suspension); tetracycline ointment (tetracycline cream).

(a) *Standards of identity, strength, quality and purity.* Chlortetracycline hydrochloride ointment, tetracycline hydrochloride ointment, and tetracycline ointment are crystalline chlortetracycline hydrochloride, chlortetracycline calcium, tetracycline hydrochloride, or tetracycline, in a suitable and harmless ointment base. It may contain a suitable local anesthetic, cortisone, hydrocortisone, or a suitable ester of cortisone or hydrocortisone, and one or more suitable and harmless preservatives and stabilizing agents. Its moisture content is not more than 1 percent if it is chlortetracycline hydrochloride or tetracycline hydrochloride ointment. Its potency is not less than 1 milligram per gram. The chlortetracycline hydrochloride used in making the chlortetracycline hydrochloride ointment and in preparing the chlortetracycline calcium used in making the chlortetracycline calcium ointment conforms to the requirements of § 146c.201(a), except § 146c.201(a) (1), (2), (3), (4), and (5), but its potency is not less than 750 μg. per milligram. The tetracycline hydrochloride used conforms to the requirements of § 146c.218(a), except § 146c.218(a) (2), (3), (4), and (5). The tetracycline used conforms to the requirements of

§ 146c.220(a). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The ointment shall be packaged in collapsible tubes which are well-closed containers as defined by the U. S. P., or in containers of glass or plastic that are tight containers as defined by the U. S. P. Unless it is labeled solely for hospital use, each such container shall contain not more than 2 ounces, except if it is intended for ophthalmic use each such container shall contain not more than ⅛-ounce, if it is a collapsible tube, or more than ½-ounce if it is a tight container. Each such container shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practices shall be disregarded.

(c) *Labeling*—(1) *It is packaged for ophthalmic use by man or it is intended for use by man and it contains cortisone, hydrocortisone, or an ester of cortisone or hydrocortisone.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) The statement "Expiration date ----------," the blank being filled in with the date that is 48 months if it is chlortetracycline hydrochloride ointment or tetracycline hydrochloride ointment, or 24 months if it is chlortetracycline calcium ointment, after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time the drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) If it contains one or more of the active ingredients specified in paragraph (a) of this section, after the name "chlortetracycline ointment," "chlortetracycline calcium ointment," "chlortetracycline calcium cream," "tetracycline hydrochloride ointment," or "tetracycline ointment," wherever it appears, the words "with ----------," in juxtaposition with such name, the blank being filled in with the common or usual name of each such ingredient used.

(2) *It is intended for use by man; it is not packaged for ophthalmic use, and it does not contain cortisone, hydrocortisone, or an ester of cortisone or hydrocortisone.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall contain a circular or other labeling within or attached to the package bearing adequate directions and warnings for the prophylactic use of such ointment.

(3) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of ointment shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline, tetracycline hydrochloride or tetracycline used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that each component of the ointment base used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The chlortetracycline hydrochloride or tetracycline hydrochloride or tetracycline used in making the batch; potency, moisture, pH, crystallinity, and absorptivity, if it is tetracycline hydrochloride or tetracycline.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one package for each 5,000 packages in the batch, but in no case less than five packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline, tetracycline hydrochloride or tetracycline used in making the batch; ten packages, containing approximately equal portions of not less than 60 milligrams each, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each component of the ointment base, each containing approximately 200 grams; 1 package of each preservative used, each containing approximately 5 grams; and if cortisone, hydrocortisone, or an ester of cortisone or hydrocortisone is used, 1 package of such ingredient, containing approximately 100 milligrams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of ointment under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.203 Chlortetracycline troches (chlortetracycline hydrochloride troches); tetracycline hydrochloride troches.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline troches and tetracycline hydrochloride troches are troches composed of crystalline chlortetracycline or crystalline tetracycline hydrochloride and one or more suitable and harmless diluents, binders, and lubricants, with or without one or more suitable and harmless preservatives, colorings, and flavorings. The potency of each troche is not less than 5 milligrams; the moisture content is not more than 2 percent. The chlortetracycline used conforms to the requirements of §146c.201 (a), except § 146c.201 (a) (1), (2), (4) and (5), but its potency is not less than 750 micrograms per milligram. The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a), except § 146c.218 (a) (2), (4) and (5). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each troche is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the troches by a plug of cotton or other like material. The composition of the immediate container, or foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106

(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months, or 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after being stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by paragraph (a) of this section.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of troches shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline or tetracycline hydrochloride used in making such batch was completed, the number of milligrams in each troche, the quantity of each ingredient used in making the batch, the date on which the latest assay of the troches comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per troche and average moisture.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; purity, toxicity, moisture, pH, crystallinity, and absorptivity if it is tetracycline hydrochloride.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one troche for each 5,000 troches in the batch, but in no case less than 30 troches, collected by taking single troches at such intervals throughout the entire time the troches are being made that the quantities made during the intervals are approximately equal.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of troches under the regulations in this part shall be:

(1) $0.75 for each troche in the sample submitted in accordance with paragraph (d) (3) (i) of this section, $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such troches, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.204 Chlortetracycline hydrochloride capsules; tetracycline hydrochloride capsules; tetracycline capsules; tetracycline phosphate complex capsules.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline hydrochloride capsules, tetracycline hydrochloride capsules, tetracycline capsules and tetracycline phosphate complex capsules are capsules composed of crystalline chlortetracycline hydrochloride, tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex, with or without one or more suitable sulfonamides, analgesic substances, antihistaminics, and with or without one or more suitable and harmless vitamin substances, buffer substances, vegetable oils, preservatives, diluents, binders, lubricants, colorings, and flavorings and glucosamine hydrochloride, enclosed in a gelatin capsule. Each capsule shall contain not less than 50 milligrams of chlortetracycline hydrochloride, tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex, unless it is intended solely for veterinary use and is conspicuously so labeled. Its moisture content is not more than 2 percent if it contains chlortetracycline hydrochloride, not more than 3 percent if it contains tetracycline (not more than 9 percent if it contains sodium metaphosphate as a buffer substance), not more than 4 percent if it contains tetracycline hydrochloride, and not more than 9 percent if it contains tetracycline phosphate complex, except that in no case shall it be more than 3 percent if it contains vitamins. The chlortetracycline hydrochloride used conforms to the requirements of § 146c.201 (a), except § 146c.201 (a) (2), (4), and (5). The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a), except § 146c.218 (a) (2), (4), and (5). The tetracycline used conforms to the requirements of § 146c.220 (a). The tetracycline phosphate complex used conforms to the requirements of § 146c.232. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each capsule is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the capsules by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date _____," the blank being filled in with one of the following dates after the month during which the batch was certified:

(*a*) If chlortetracycline hydrochloride is used, 60 months.

(*b*) If tetracycline hydrochloride is used, 48 months, except that the date that is 60 months may be used if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by paragraph (a) of this section.

(*c*) If tetracycline is used, 36 months.

(*d*) If tetracycline phosphate complex is used, or if it contains one or more vitamin substances, analgesic substances, antihistaminics, or caffeine, 24 months, except that the blank may be filled in with the date that is 36 months, 48 months, or 60 months, after the month in which the batch was certified, if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(*e*) If it contains sodium metaphosphate, 36 months.

(ii) If it contains, in addition to chlortetracycline hydrochloride, tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex, one or more of the active ingredients specified in paragraph (a) of this section, after the name "chlortetracycline hydrochloride capsules," "tetracycline hydrocloride capsules," "tetracycline capsules," or "tetracycline phosphate complex capsules," wherever it appears, the words "with _____ (the blank being filled

in with the common or usual name of each other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline, tetracycline hydrochloride, tetracycline or tetracycline phosphate complex used in making such batch was completed, the number of milligrams in each capsule, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per capsule and average moisture.

(ii) The chlortetracycline, tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex used in making the batch: Potency, toxicity, moisture, pH, crystallinity, absorptivity (if it is tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex), and identity if it is tetracycline phosphate complex.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one capsule for each 5,000 capsules in the batch, but in no case less than 30 capsules, collected by taking single capsules at such intervals throughout the entire time of preparation that the quantities encapsulated during the intervals are approximately equal.

(ii) The chlortetracycline, tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, and if it is tetracycline phosphate complex, one additional package containing approximately 1 gram. Each such package shall be packaged in accordance with the requirements of § 146c.201(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $0.75 for each capsule in the sample submitted in accordance with paragraph (d) (3) (i) of this section, $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such capsules and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.205 Chlortetracycline powder (chlortetracycline hydrochloride powder); tetracycline hydrochloride powder; tetracycline powder.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline powder, tetracycline hydrochloride powder, and tetracycline powder are crystalline chlortetracycline hydrochloride, tetracycline hydrochloride, or tetracycline, with or without glucosamine hydrochloride and one or more suitable and harmless vitamin substances, with or without one or more suitable analgesic substances and antihistaminics, and with or without suitable and harmless buffer substances, preservatives, diluents, colorings, and flavorings. The content of chlortetracycline or tetracycline hydrochloride or tetracycline is not less than 15 milligrams per gram of powder. The moisture content of chlortetracycline powder or tetracycline hydrochloride powder is not more than 2 percent. The moisture content of tetracycline powder is not more than 7.5 percent. The chlortetracycline used conforms to the requirements of § 146c.201 (a), except § 146c.201 (a) (2), (4), and (5). The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a), except subparagraphs (2), (4), and (5) of that paragraph. The tetracycline used conforms to the requirements of § 146c.220 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date _____," the blank being filled in with the date that is 60 months after the month during which the batch was certified if it is chlortetracycline hydrochloride powder; or if it is tetracycline hydrochloride powder or tetracycline powder the blank is filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section; except that if it contains one or more vitamin substances, analgesic substances, or antihistaminics, the blank is filled in with the date that is 24 months after the month during which the batch was certified.

(ii) If it contains, in addition to chlortetracycline hydrochloride, tetracycline hydrochloride, or tetracycline, one or more of the other active ingredients specified in paragraph (a) of this section, after the name "chlortetracycline powder," "tetracycline hydrochloride powder," or "tetracycline powder," wherever such name appears, the words "with _____ (the blank being filled in with the common or usual name of each other such ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline, tetracycline hydrochloride or tetracycline used in making such batch was completed, the number of milligrams in each immediate container, the quantity of each ingredient used in making the batch, the date on which

the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The chlortetracycline, tetracycline hydrochloride, or tetracycline used in making the batch; potency, toxicity, moisture, pH, crystallinity, and absorptivity if it is tetracycline hydrochloride or tetracycline.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 containers in the batch, but in no case less than 5 immediate containers, unless each such container is packaged to contain more than 1.0 gram, in which case the sample shall consist of 1.0 gram for each 5,000 immediate containers in the batch, but in no case less than five 1.0-gram portions, except if it is intended for use as an ingredient in the drinking water of animals, each portion in the sample submitted shall consist of 1 ounce in lieu of 1.0 gram. Such sample shall be collected by taking single immediate containers, 1.0-gram portions, or 1-ounce portions at such intervals throughout the entire time the containers are being filled that the quantities filled during the intervals are approximately equal.

(ii) The chlortetracycline, tetracycline hydrochloride, or tetracycline used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of chlortetracycline powder for veterinary use, tetracycline hydrochloride powder for veterinary use, and tetracycline powder for veterinary use from certification.* Chlortetracycline powder, tetracycline hydrochloride powder, and tetracycline powder that conform to the requirements of paragraphs (a) (except that if they contain one or more added vitamin substances such substances are essential for nutritive purposes, and except that they may contain one or more added mineral substances essential for nutritive purposes), (b), and (c) of this section shall be exempt from the requirements of sections 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) They are intended solely for veterinary use and are conspicuously so labeled.

(2) If they contain added vitamins or minerals, the labels bear the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The labels bear an expiration date that is not more than 60 months, or 24 months if it contains a vitamin substance, after the month during which the batch was last assayed and released by the manufacturer.

(4) The labels bear a statement that solutions prepared with the drugs are stable for not more than 24 hours.

(5) The circular or other labeling within or attached to the package bears information that only the antibiotics are intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Pinkeye and superficial cuts and abrasions.

(ii) Bacterial enteritis in swine.

(iii) Bacterial pneumonia in swine.

(iv) Chronic respiratory disease (airsac infection), hexamitiasis, blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(v) Infectious sinusitis in poultry.

(vi) Synovitis in poultry.

(vii) Bacterial pneumonia in calves.

(viii) Shipping fever (hemorrhagic septicemia) in calves.

§ 146c.206 Chlortetracycline ophthalmic (chlortetracycline hydrochloride ophthalmic); tetracycline hydrochloride ophthalmic.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline ophthalmic and tetracycline hydrochloride ophthalmic is crystalline chlortetracyline or crystalline tetracycline hydrochloride, with or without one or more suitable and harmless preservatives, buffer substances, and diluents. It is sterile. Its moisture content is not more than 5 percent. The chlortetracycline or tetracycline hydrochloride is of such quantity that when dissolved as directed the potency of such solution is not less than 1,000 micrograms per milliliter and maintains its labeled potency after it has been kept for 7 days at a temperature of 15° C. (59° F.). Such solution has a pH of not less than 7.9 and not more than 8.4. The chlortetracycline used conforms to the requirements of § 146c.201 (a) except subparagraphs (2), (4), and (5) and the tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a) except subparagraphs (2), (4), and (5). Each other buffer and diluent used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container shall be a tight container as defined by the U. S. P.; its closure shall be one through which a hypodermic needle cannot be introduced; and the container shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not less than 5 milligrams, and each may be packaged in combination with a container of the solvent, sterile distilled water U. S. P.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 48 months, if it is chlortetracycline ophthalmic; or if it is tetracycline hydrochloride ophthalmic, the blank is filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time, such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for clarification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless previously submitted) the date on which the latest assay of the chlortetracycline or tetracycline hydrochloride used in mak-

ing such batch was completed, the number of milligrams in each immediate container, the quantity of each buffer and diluent used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each buffer and diluent used in making the batch conform to the requirements prescribed therefor, if any, by this section. If such batch or any part thereof is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture, and pH of the solution prepared as directed in its labeling.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; potency, toxicity, moisture, pH, crystallinity, and absorptivity, if it is tetracycline hydrochloride.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; ten packages, each containing approximately equal portions of not less than 60 milligrams packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, each buffer and diluent used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.207 Chlortetracycline hyrdochloride tablets; tetracycline hydrochloride tablets; tetracycline tablets.

(a) Chlortetracycline hydrochloride tablets, tetracycline hydrochloride tablets, and tetracycline tablets are tablets that conform to all requirements and are subject to all procedures prescribed by § 146c.204 for chlortetracycline hydrochloride capsules, tetracycline hydrochloride capsules, and tetracycline capsules, except that the average moisture content of the tablets is not more than 3.0 percent. In addition to the requirements prescribed by § 146c.204, tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. A person who requests certification shall therefore also submit for disintegration-time studies, results of this test made by him and a sample of 6 tablets. The fee for the tablets submitted for disintegration-time studies shall be $3.00.

(b) *Exemption of chlortetracycline hydrochloride tablets from certification.* Chlortetracycline hydrochloride tablets that conform to the requirements of paragraph (a) of this section (except that it may contain one or more essential vitamin and mineral substances for nutritive purposes; and the chlortetracycline hydrochloride used in making the tablets may conform to § 146c.219 (a)) shall be exempt from the requirements of sections 502 (1) and 507 of the act, if they comply with all the following conditions:

(1) If the drug contains added vitamins or minerals, its label bears the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while the birds are eating less feed.

(2) The labels bear an expiration date that is not more than 24 months after the month during which the batch was last assayed and released by the manufacturer.

(3) The label bears a statement that solutions prepared with the drug are stable for not more than 24 hours.

(4) The circular or other labeling within or attached to the package bears information that only the antibiotic is intended for use in the prevention or treatment of the following conditions of parakeets and canaries, due to organisms sensitive to chlortetracycline, and further, bears directions and warnings adequate for such uses:

(i) Respiratory disease, bacterial (pneumonia, bronchitis, rhinitis).

(ii) Infectious arthritis due to a filterable agent.

(iii) Bacterial enteritis.

(iv) Stimulate food intake, growth, and to maintain body weight.

(v) When intended for use in the conditions set forth in subdivisions (i), (ii), and (iii), of this subparagraph, the potency must be such, that when used as directed in the labeling, each ounce of drinking water contains not less than 25 milligrams of chlortetracycline.

(vi) When intended for use in the conditions set forth in subdivision (iv) of this subparagraph, the potency must be such, that when used as directed in the labeling, each ounce of drinking water contains not less than 5.0 milligrams of chlortetracycline.

§ 146c.208 Chlortetracycline otic (chlortetracycline hydrochloride otic, chlortetracycline hydrochloride for ear solution); tetracycline hydrochloride otic (tetracycline hydrochloride for ear solution).

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline otic, tetracycline otic is a packaged combination of one immediate container of crystalline chlortetracycline or crystalline tetracycline hydrochloride and one immediate container of a suitable and harmless solution. The chlortetracycline or tetracycline hydrochloride is of such quantity that when dissolved as directed the potency of such solution is not less than 5 milligrams per milliliter after it has been kept for 7 days at a temperature of 15° C. (59° F.). The chlortetracycline used conforms to the requirements of § 146c.201(a), except § 146c.201(a) (2), (3), (4), and (5). The tetracycline hydrochloride used conforms to the requirements of § 146c.218(a), except § 146c.218(a) (2), (3), (4), and (5). Each substance used in the preparation of the solution contained in the packaged combination, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Each immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and on the immediate container of the chlortetracycline or tetracycline hydrochloride, the statement "Expiration date ----------," the blank being filled in with the date that is 36 months after the month during which the batch was certified.

(ii) On the outside wrapper or container and on the immediate container of the solution in the packaged combination, a statement giving the method of dissolving the chlortetracycline or tetracycline hydrochloride in the solution and the conditions under which the solution

should be stored, including reference to its instability when stored under other conditions, and the statement, "The solution may be kept in a refrigerator for 1 week without significant loss of potency."

(2) *It is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the number of milligrams in each immediate container thereof, the date on which the latest assay of the batch was completed, the batch mark, and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline or tetracycline hydrochloride used in making such batch was completed, the quantity of each ingredient used in making the solution included in the packaged combination, and a statement that such solution conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The solution after the chlortetracycline or tetracycline hydrochloride has been disolved therein; potency.

(iii) The chlortetracycline or tetracycline hydrochloride used in making the batch; potency, moisture, pH, crystallinity, and absorptivity if it is tetracycline hydrochloride.

(3) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one package for each 5,000 packages in the batch, but in no case less than 5 packages, collected by taking a single package at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, or when any change is made in composition of such solution; 5 packages of the solution included in the combination.

(4) No result referred to in subparagraph (2) (iii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigation.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.209 Chlortetracycline dental cones (chlortetracycline hydrochloride dental cones).

Chlortetracycline dental cones conform to all requirements prescribed by § 146c.203 for chlortetracycline troches, and are subject to all procedures prescribed by § 146c.203 for chlortetracycline troches, except that they may contain a suitable local anesthetic.

§ 146c.210 Chlortetracycline dental paste (chlortetracycline hydrochloride dental paste).

Chlortetracycline dental paste conforms to all requirements prescribed by § 146c.202 for chlortetracycline ointment, and is subject to all procedures prescribed by § 146c.202 for chlortetracycline ointment, except that:

(a) Its potency is not less than 30 milligrams per gram.

(b) Its moisture content is not more than 3 percent.

(c) It contains one or more suitable and harmless binders, and it may contain one or more suitable and harmless colorings and flavorings.

(d) It is packaged in immediate containers of glass which meet the tests for tight containers as defined by the U. S. P.

§ 146c.211 Chlortetracycline surgical powder (chlortetracycline hydrochloride surgical powder); tetracycline hydrochloride surgical powder.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline surgical powder and tetracycline hydrochloride surgical powder are crystalline chlortetracycline or crystalline tetracycline hydrochloride, with or without suitable and harmless diluents, preservatives, and lubricants. The content of chlortetracycline or tetracycline hydrochloride is not less than 50 milligrams per gram of powder. It is sterile. Its moisture content is not more than 2 percent.[1] The chlortetracycline used conforms to the requirements of § 146c.201(a), except § 146c.201(a) (4) and (5). The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a), except § 146c.218(a) (4) and (5). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed (unless it contains inert gases) that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity thereof beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container may contain one or more suitable and harmless inert gases.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 60 months after the month during which the batch was certified if it is chlortetracycline hydrochloride surgical powder, or with the date that is 24 months after the month during which the batch was certified if it is tetracycline hydrochloride surgical powder, except that if the person who requests certification has submitted to the Commissioner results of tests and assays that show such drug as prepared by him is stable for 36 months, 48 months, or 60 months, such date may be used for such drug.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(3) On the circular or other labeling within or attached to the package, if it is packaged for dispensing and it is intended solely for veterinary use and is conspicuously so labeled, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the

chlortetracycline or tetracycline hydrochloride used in making such batch was completed, the number of milligrams of chlortetracycline or tetracycline hydrochloride in each immediate container, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; potency, sterility, toxicity, moisture, pH, crystallinity, and absorptivity if it is tetracycline hydrochloride.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: One immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers (or if it is packaged with inert gases, not less than 7 immediate containers), collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch.

(*a*) For all tests except sterility: 10 packages each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(*b*) For sterility testing: 10 immediate containers.

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (ii) (*b*) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.212 Chlortetracycline suppositories (chlortetracycline hydrochloride suppositories); tetracycline hydrochloride suppositories.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline suppositories and tetracycline hydrochloride suppositories are suppositories composed of crystalline chlortetracycline or tetracyline hydrochloride in a suitable and harmless base, with or without one or more suitable and harmless preservatives. The potency of each suppository is not less than 100 milligrams, except if it is intended for rectal use its potency is not less than 50 milligrams. Its moisture content is not more than 1 percent. The chlortetracycline used conforms to the requirements of § 146c.201 (a), except § 146c.201 (a) (1), (2), (3), (4), and (5), but its potency is not less than 750 micrograms per milligram. The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a), except § 146c.218 (a) (2), (3), (4), and (5). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its outside wrapper or container and the immediate container the statement "Expiration date ----------," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time, such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(3) On the circular or other labeling within or attached to the package, if it is packaged for dispensing and it is intended solely for veterinary use and is conspicuously so labeled, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline or tetracycline hydrochloride used in making such batch was completed, the number of milligrams of chlortetracycline or tetracycline hydrochloride in each suppository, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per suppository and moisture.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; potency, moisture, pH, crystallinity, and absorptivity if it is tetracycline hydrochloride.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one suppository for each 5,000 suppositories in the batch, but in no case less than 30 suppositories, collected by taking single suppositories at such intervals throughout the entire time the suppositories are being made that the quantities made during the intervals are approximately equal.

(ii) The chlortetracycline or tetracycline hydrochloride used in making the batch; 10 packages, each containing approximately equal portions of not less

than 60 milligrams, packaged in accordance with § 146c.201 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $0.75 for each suppository in the samples submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.213 Chlortetracycline gauze packing (chlortetracycline hydrochloride gauze packing).

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline gauze packing is absorbent gauze that is impregnated with crystalline chlortetracycline. Its content of chlortetracycline is not less than 4 milligrams per gram and not less than 1.0 milligram per linear foot of gauze. It is sterile. Its moisture content is not more than 5 percent. The chlortetracycline used conforms to the standards prescribed therefor by § 146c.-201(a), except subparagraphs (2), (4), and (5) of that paragraph. The absorbent gauze used conforms to the standards prescribed therefor by the U.S.P.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 36 months after the month during which the batch was certified.

(ii) On the immediate container, the statement "Sterility cannot be guaranteed if the package bears evidence of damage or has been previously opened."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chlortetracycline gauze packing shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline used in making such batch was completed, the potency of each gram and of each linear foot of the gauze packing, the date on which the latest assay of the batch was completed, and a statement that the absorbent gauze used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per gram and per linear foot of the gauze packing, sterility, and average moisture.

(ii) The chlortetracycline used in making the batch; potency, toxicity, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: one package for each 5,000 packages in the batch, but in no case less than 5 packages.

(*b*) For sterility testing: 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline used in making the batch; ten packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, one package consisting of approximately 5 linear yards, or the equivalent, of the absorbent gauze used.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations other than examination of such chlortetracycline gauze packing and packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.214 Chlortetracycline dressing (chlortetracycline hydrochloride dressing).

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline dressing is absorbent gauze impregnated with chlortetracycline ointment. Each square inch of such dressing shall contain not less than 2 milligrams of chlortetracycline. It is sterile. Its moisture content is not more than 5 percent. The chlortetracycline ointment used conforms to the standards prescribed for chlortetracycline ointment by § 146c.202 (a), except that its potency is not less than 20 milligrams per gram. The absorbent gauze used conforms to the standards prescribed therefor by the U.S.P.

(b) *Packaging.* In all cases the immediate container for each chlortetracycline dressing shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) On the immediate container, the statement "Sterility cannot be guaranteed if package bears evidence of damage or has been previously opened."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subpara-

graph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chlortetracycline dressings shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline used in making such batch was completed, the number of grams of chlortetracycline ointment contained in each dressing of the batch and its potency per gram, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency of chlortetracycline per dressing, sterility, and average moisture.

(ii) The chlortetracycline used in making the batch; potency, toxicity, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one dressing for each 5,000 dressings in the batch, but in no case less than 5 dressings.

(*b*) For sterility testing; 10 dressings.

Such samples shall be collected by taking single dressings at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, one package consisting of approximately five linear yards, or the equivalent, of the absorbent gauze used.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), and (iii) of this section; $10.00 for all immediate containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations other than examination of such dressings and packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.215 Chlortetracycline with vasoconstrictor (chlortetracycline hydrochloride with vasoconstrictor); chlortetracycline with _____ (chlortetracycline hydrochloride with _____) (the blank being filled in with the common or usual name of the vasoconstrictor).

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline with vasoconstrictor is a dry mixture of crystalline chlortetracycline and a suitable vasoconstrictor, with or without suitable and harmless diluents, preservatives, colorings, and flavorings, or it is a packaged combination of one immediate container of crystalline chlortetracycline with or without suitable and harmless diluents, preservatives, colorings, and flavorings and one immediate container of a solution of a suitable vasoconstrictor. The chlortetracycline is of such quantity that when dissolved as directed the potency of such solution is not less than 1 milligram per milliliter and maintains its labeled potency after it has been kept for 4 days in a refrigerator. Such solution has a pH of not less than 2.75 and not more than 3.3. The moisture content of the dry mixture is not more than 5.0 percent. The chlortetracycline used conforms to the requirements of § 146c.201 (a), except subparagraphs (2), (4), and (5) of that paragraph. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Each immediate container shall be a tight container as defined by the U. S. P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container of chlortetracycline, the statement "Expiration date _____," the blank being filled in with the date that is 36 months after the month during which the batch was certified.

(ii) On the outside wrapper or container and on the immediate container of the solution in the packaged combination, a statement giving the method of dissolving the chlortetracycline.

(iii) On the outside wrapper or container and on the immediate container in which the finished drug is prepared for use, the conditions under which the solution should be stored, including a reference to its instability when stored under other conditions, and the statement "The solution may be kept in a refrigerator for 4 days without significant loss of potency."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chlortetracycline with vasoconstrictor shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the number of milligrams of chlortetracycline in such immediate container, and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline used in making such batch was completed, the quantity of each ingredient used in making the batch, the quantity of each ingredient used in making the solution included in the packaged combination, and a statement that such solution conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and average moisture.

(ii) The chlortetracycline used in making the batch; potency, toxicity, moisture, pH, and crystallinity.

(3) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the

quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline used in making the batch; 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(iv) In case of an initial request for certification of the packaged combination of chlortetracycline with vasoconstrictor, or when any change is made in the composition of such solution; five packages of the solution included in the combination.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container or package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), (iii), and (iv) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.216 Tetracycline hydrochloride-oleandomycin ointment.

Tetracycline hydrochloride-oleandomycin ointment conforms to all requirements and is subject to all procedures prescribed by § 146c.202 for tetracycline hydrochloride ointment, except that:

(a) Each gram contains not less than 3.33 milligrams of tetracycline hydrochloride and not less than 1.67 milligrams of oleandomycin as the base or as the phosphate salt. The crystalline oleandomycin base used is produced by the growth of Streptomyces antibioticus; its potency is not less than 850 μg. per milligram; it is nontoxic; its moisture content is not more than 5.0 percent; its pH in an aqueous suspension containing 100 milligrams per milliliter is not less than 9.0 and not more than 10.5. The crystalline oleandomycin phosphate used conforms to the standards prescribed by § 146c.231 (a) (1).

(b) In no case shall the drug be exempt from the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), if it is intended for use by man.

(c) In addition to complying with the requirements of § 146c.202 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the oleandomycin base or oleandomycin phosphate used in making the batch for potency, toxicity, moisture, pH, and crystallinity. He shall also submit in connection with his request a sample consisting of not less than 6 packages of such ointment and (unless previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the oleandomycin used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) (3) of this section shall be:

(1) $5.00 for each immediate container of the ointment.

(2) $4.00 for each immediate container of the oleandomycin.

§ 146c.217 Chlortetracycline calcium syrup (chlortetracycline calcium oral drops); tetracycline syrup (tetracycline oral drops); tetracycline magnesium syrup (tetracycline magnesium oral drops).

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline calcium syrup, tetracycline syrup, and tetracycline magnesium syrup are syrups that contain chlortetracycline calcium prepared from crystalline chlortetracycline hydrochloride, tetracycline, or tetracycline magnesium prepared from tetracycline or tetracycline hydrochloride with or without one or more suitable sulfonamides, analgesic substances, antihistaminics, caffeine, glucosamine hydrochloride, *N*-acetylglucosamine, and one or more suitable and harmless buffer substances, suspending and stabilizing agents, and preservatives, suspended in a suitable and harmless vehicle. Each milliliter shall contain a quantity of chlortetracycline calcium or tetracycline or tetracycline magnesium equivalent to not less than 25 milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride. The pH is not less than 6.5 nor more than 9.0, except if it is tetracycline syrup the pH is not less than 3.5 nor more than 6.0, except if it contains *N*-acetylglucosamine the pH is not less than 5.0 and not more than 7.5. The crystalline chlortetracycline hydrochloride used conforms to the requirements of § 146c.201(a), except § 146c.201 (a) (2), (4), and (5). The crystalline tetracycline used conforms to the requirements of § 146c.220. The tetracycline hydrochloride used conforms to the requirements of § 146c.218(a) except § 146c.218(a) (2), (4), and (5). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except the blank may be filled in with the date that is 18 months, 24 months, 36 months, or 48 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) If it contains, in addition to chlortetracycline calcium, tetracycline, or tetracycline magnesium, one or more of the other active ingredients specified in paragraph (a) of this section, after the name "chlortetracycline calcium syrup" or "tetracycline syrup" or "tetracycline magnesium syrup," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of such other ingredient)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline hydrochloride or tetracycline or tetracycline hydrochloride used in making such batch was completed, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per milliliter, pH, and toxicity if it is

chlortetracycline calcium syrup or tetracycline magnesium syrup.

(ii) The chlortetracycline hydrochloride or tetracycline or tetracycline hydrochloride used in making the batch; potency, toxicity, moisture, pH, crystallinity, and absorptivity if it is tetracycline or tetracycline hydrochloride.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one package for each 5,000 packages in the batch, but in no case less than 5 packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline hydrochloride or tetracycline or tetracycline hydrochloride used in making the batch; 10 packages each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.218 Tetracycline hydrochloride.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride is the crystalline hydrochloride salt of the deschloro derivative of a kind of chlortetracycline or a mixture of two or more such salts, with or without one or more suitable and harmless stabilizing agents. It is so purified and dried that:

(1) Its potency, and the potency of the tetracycline hydrochloride used in the manufacture of tetracycline hydrochloride intended for use by injection, is not less than 900 micrograms per milligram.

(2) It is sterile.

(3) It is nontoxic.

(4) It is nonpyrogenic.

(5) It contains no histamine nor histamine-like substance.

(6) Its moisture content is not more than 2 percent.

(7) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 1.8 and not more than 2.8, except if it is intended for use by injection its pH is not less than 2.0 and not more than 3.0.

(8) Its absorptivity and the absorptivity of the tetracycline hydrochloride used in the manufacture of tetracycline hydrochloride intended for use by injection is 100±4 percent of the tetracycline hydrochloride working standard similarly treated and both calculated on the anhydrous basis.

(b) *Packaging; labeling; request for certification, check tests and assays, samples; fees.* Tetracycline hydrochloride conforms to all requirements and procedures prescribed for chlortetracycline hydrochloride by § 146c.201 (b), (c), (d), and (e), except that:

(1) It shall be labeled with an expiration date that is 36 months after the month during which the batch was certified, except that it may be labeled with the date that is 48 months or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) The person who requests certification of a batch of tetracycline hydrochloride that contains stabilizing agents and is intended for use by injection shall submit with his request (unless they were previously submitted) the results of the latest tests and assays made on the batch of the tetracycline hydrochloride used in making such batch for potency and absorptivity and a sample consisting of two packages each containing approximately 500 milligrams of the tetracycline hydrochloride used in making such batch for potency and absorptivity.

(3) The fee for the services rendered with respect to each immediate container of the tetracycline hydrochloride used in the manufacture of a batch of tetracycline hydrochloride intended for use by injection submitted in accordance with the requirements prescribed therefor by subparagraph (2) of this paragraph shall be $4.00.

§ 146c.219 Crude chlortetracycline oral veterinary.

(a) *Standards of identity, strength, quality, and purity.* Crude chlortetracycline oral veterinary is crude chlortetracycline with suitable and harmless diluents, buffer substances, and suspending or dispersing agents. It contains not less than 2 grams of chlortetracycline activity per pound. Its moisture content is not more than 6 percent.

(b) *Packaging.* In all cases the immediate container shall be a well-closed container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not more than 100 pounds.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of grams of chlortetracycline in each pound of the batch.

(iii) The statement "For oral veterinary use only."

(iv) The statement "Expiration date _____," the blank being filled in with the date which is 24 months after the month during which the batch was certified.

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the number of grams of chlortetracycline in each pound of the batch, and the quantity of each other ingredient used in making the batch, and the date on which the latest assay of the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for average potency and average moisture.

(2) Such person shall submit in connection with his request a sample of the batch consisting of 1 ounce for each 3,000 pounds in the batch, but in no case less than five 1-ounce portions, collected by taking single 1-ounce portions at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than examination of such drug are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit main-

tained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of crude chlortetracycline oral veterinary from certification.* Crude chlortetracycline oral veterinary that conforms to the requirements of paragraphs (a) (except that it may contain one or more essential vitamin and mineral substances for nutritive purposes), (b), and (c) of this section shall be exempt from the requirements of sections 502 (l) and 507 of the act, if it complies with all the following conditions:

(1) If it contains added vitamins or minerals, its label bears the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(2) The label bears an expiration date that is not more than 12 months after the month during which the batch was last assayed and released by the manufacturer.

(3) The label bears a statement that solutions prepared with the drug are stable for not more than 24 hours.

(4) The circular or other labeling within or attached to the package bears information that only the antibiotic is intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Bacterial enteritis in swine.

(ii) Bacterial pneumonia in swine.

(iii) Chronic respiratory disease (air-sac infection), hexamitiasis, blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(iv) Infectious sinusitis in poultry.

(v) Synovitis in poultry.

(vi) Bacterial pneumonia in calves.

(vii) Shipping fever (hemorrhagic septicemia) in calves.

§ 146c.220 Tetracycline.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline is the hydrated or anhydrous crystalline compound of the deschloro derivative of a kind of chlortetracycline, or a mixture of two or more such compounds. It is so purified that:

(1) Its potency is not less than 975 micrograms per milligram on the anhydrous basis.

(2) It is nontoxic.

(3) Its moisture content is not more than 13 percent.

(4) Its pH in an aqueous suspension prepared by adding 10 milligrams per milliliter is not less than 3.0 and not more than 7.0.

(5) Its absorptivity at 380 mμ, calculated on the anhydrous basis, is 108.2±3.75 percent of the tetracycline hydrochloride working standard treated as described in § 141c.218(e) and calculated on the anhydrous basis.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of tetracycline shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of micrograms of tetracycline per milligram expressed in terms of its equivalency of tetracycline hydrochloride, and the total number of grams in the immediate container.

(3) The statement "Expiration date _____," the blank being filled in with the date which is 36 months after the month during which it was certified.

(4) The statement "For use only in the manufacture of nonparenteral drugs."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, crystallinity, and absorptivity.

(2) Such person shall submit with his request an accurately representative sample of the batch consisting of 10 packages, each containing approximately 60 milligrams taken from a different part of such batch and each packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which tetracycline is to be used, the manufacturer of the batch that is to be so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer the results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) and (3) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations. The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.221 Tetracycline hydrochloride for intramuscular use; tetracycline phosphate complex for intramuscular use.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride or tetracycline phosphate complex for intramuscular use is a dry mixture of tetracycline hydrochloride or tetracycline phosphate complex, magnesium chloride or magnesium ascorbate and one or more suitable buffer substances, with or without one or more suitable preservatives and anesthetic agents, and with or without one or more suitable and harmless vitamin substances. It is sterile. It is nonpyrogenic. Its moisture content is not more than 5 percent. Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2.0 and not more than 3.0. The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a). The tetracycline phosphate complex used conforms to the requirements of § 146c.232 (a) and it contains no histamine or histamine-like substance. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The immediate containers shall be of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container shall contain not less than the equivalent of 100 milligrams of tetracycline hydrochloride, and each may be packaged in combination with a container of a suitable and harmless diluent.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months (if it contains tetracycline phosphate complex) or 36 months (if it contains tetracycline hydrochloride) after the month during which the

batch was certified, except that the blank may be filled in with the date that is 48 months or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section, and except that the blank is filled in with the date that is 12 months after the month during which the batch was certified if it contains one or more vitamin substances.

(ii) If it contains one or more vitamin substances, after the name "tetracycline hydrochloride for intramuscular use" or "tetracycline phosphate complex for intramuscular use," the words "with vitamin _____" (the blank being filled in with the name of the vitamin ingredient used), or "with vitamins" (if it contains more than one vitamin ingredient), in juxtaposition with such name.

(iii) On the circular or other labeling within or attached to the package, a statement of the conditions under which solutions prepared from the drug should be stored and the statement "Sterile solutions may be stored at room temperature for 24 hours without significant loss of potency," except that if it contains one or more vitamin substances it shall bear the statement "Inject immediately after the solution is prepared from the drug."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the tetracycline hydrochloride or tetracycline phosphate complex used in making such batch was completed, the equivalent number of milligrams of tetracycline hydrochloride in each package, the date on which the latest assay of the drug comprising the batch was completed, the quantity of each other ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section. If such batch or any part thereof is to be packaged with a diluent, such request shall also be accompanied by a statement that such diluent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request the results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency, sterility, pyrogens, moisture, pH.

(ii) The tetracycline hydrochloride or tetracycline phosphate complex used in making the batch: Potency, toxicity, histamine, absorptivity, crystallinity, and identity if it is tetracycline phosphate complex.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The tetracycline hydrochloride or tetracycline phosphate complex used in making the batch: 10 packages, each containing approximately equal portions of not less than 250 milligrams, and if it is tetracycline phosphate complex, one additional package containing approximately 1 gram. Each such package shall be packaged in accordance with the requirements of § 146c.201(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each, containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch which is to be packaged in combination with a diluent that is not recognized by the U. S. P. or when any change is made in the composition of such diluent: 5 packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility: 10 packages, each containing approximately 0.25 gram.

(ii) For sterility testing: 10 packages, each containing approximately 40 milligrams of tetracycline hydrochloride or tetracycline phosphate complex.

Each such package shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), (iii), (iv), and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (4) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.222 Tetracycline hydrochloride oral suspension (tetracycline hydrochloride homogenized mixture); tetracycline phosphate complex oral suspension (tetracycline phosphate complex oral drops); tetracycline hydrochloride oral solution; tetracycline calcium oral suspension; tetracycline oral suspension.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride oral suspension, tetracycline hydrochloride oral solution, and tetracycline calcium oral suspension are tetracycline hydrochloride or tetracycline calcium prepared from tetracycline hydrochloride. Tetracycline oral suspension and tetracycline phosphate complex oral suspension are prepared from tetracyline or tetracycline phosphate complex. Each drug contains one or more suitable and harmless suspending and dispersing agents (unless it is tetracycline hydrochloride oral solution), with or without one or more suitable sulfonamides, and with or without one or more suitable and harmless colorings, flavorings, buffer substances, and preservatives, suspended or dissolved in a suitable and harmless vehicle. If it is tetracycline hydrochloride oral suspension, tetracycline oral suspension, or tetracycline phosphate complex oral suspension, it may contain one or more suitable and harmless vitamin substances. Each milliliter shall contain not less than the equivalent of 25 milligrams of tetracycline hydrochloride. Its moisture content is not more than 2 percent if it is tetracycline hydrochloride oral suspension, tetracycline phosphate complex oral suspension, or tetracycline oral suspension and not more than 7 percent if it is tetracycline hydrochloride oral solution. Its pH is not less than 2.0 and not more than 3.5 if it is tetracycline hydrochloride oral solution and not less than 7.0 and not more than 8.0 if it is tetracycline calcium oral suspension. The tetracycline hydrochloride used conforms to the standards prescribed by § 146c.218 (a), except § 146c.218 (a) (2), (4), and (5). The tetracycline phosphate complex used conforms to the standards prescribed by § 146c.232 (a). The tetracycline used conforms to the standards prescribed by § 146c.220 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container shall be a tight container as defined by the U. S. P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section, and except if it contains one or more vitamin substances the blank is filled in with the date that is 12 months after the month during which the batch was certified.

(ii) If it is tetracycline hydrochloride oral suspension, tetracycline oral suspension, or tetracycline phosphate complex oral suspension, and it contains one or more vitamin substances or sulfonamides, after the name "tetracycline hydrochloride oral suspension," "tetracycline oral suspension," or "tetracycline phosphate complex oral suspension," wherever it appears, the words "with sulfonamide(s)" or "with vitamin _____," the blank being filled with the name of the vitamin ingredient used, or "with vitamins," if it contains more than one vitamin ingredient, in juxtaposition with such name.

(iii) If it is tetracycline hydrochloride oral solution or tetracycline calcium oral suspension and it contains one or more sulfonamides, after the name "tetracycline hydrochloride oral solution" or "tetracycline calcium oral suspension," wherever it appears, the words "with sulfonamide(s)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex used in making such batch was completed, the potency per milliliter of the batch, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, each person shall submit in connection with his request results of the tests and assays listed after each of the following made by him on an accurately representative sample of:

(i) The batch: Average potency per milliliter, average moisture if it is tetracycline hydrochloride oral suspension, tetracycline oral suspension, tetracycline phosphate complex oral suspension, or tetracycline hydrochloride oral solution, and pH if it is tetracycline hydrochloride oral solution or tetracycline calcium oral suspension.

(ii) The tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex used in making the batch: Potency, toxicity, moisture, pH, crystallinity, and absorptivity, and if it is tetracycline phosphate complex, identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The tetracycline hydrochloride, tetracycline, or tetracycline phosphate complex used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, and if it is tetracycline phosphate complex, one additional package containing approximately 1 gram. Each such package shall be packaged in accordance with the requirements of § 146c.201(b).

(iii) In the case of an initial request for certification, each other ingredient used in making the batch: 1 package of each containing approximately 5.0 grams.

(4) No result referred to in subparagraph (2)(ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations other than the examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.223 Chlortetracycline-neomycin-streptomycin-penicillin ointment; chlortetracycline-neomycin-dihydrostreptomycin-penicillin ointment; tetracycline hydrochloride-neomycin-streptomycin-penicillin ointment; tetracycline hydrochloride-neomycin-dihydrostreptomycin-penicillin ointment.

(a) Chlortetracycline-neomycin-streptomycin-penicillin ointment, chlortetracycline-neomycin - dihydrostreptomycin-penicillin ointment, tetracycline hydrochloride-neomycin - streptomycin-penicillin ointment, and tetracycline hydrochloride - neomycin - dihydrostreptomycin-penicillin ointment conform to all requirements and are subject to all procedures prescribed by § 146c.202 for chlortetracycline hydrochloride ointment and tetracycline hydrochloride ointment intended solely for veterinary use, except that:

(1) They contain not less than 28 milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride per gram.

(2) They contain not less than 14 milligrams of neomycin per gram. The neomycin used conforms to the requirements prescribed by § 146e.410 (a) (2) of this chapter, except the standard for toxicity.

(3) They contain not less than 14 milligrams of streptomycin or dihydrostreptomycin per gram. The streptomycin used conforms to the standards prescribed by § 146b.101 (a) of this chapter, except § 146b.101 (a) (2), (3), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103 of this chapter, except the standards for sterility, toxicity, pyrogens, and histamine.

(4) They contain not less than 28,000 units of procaine penicillin G per gram, except that if it is intended for use by udder instillation, each single dose as recommended in its labeling contains not more than 100,000 units of procaine penicillin G. The procaine penicillin used conforms to the requirements prescribed by § 146a.44 (a) of this chapter, except § 146a.44 (a) (2), (3), and (4).

(b) Its expiration date shall be 18 months after the month during which the batch was certified.

(c) In addition to complying with the requirements of § 146c.202 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch marks and (unless they were previously submitted) the results and dates of the latest tests and

assays of the neomycin, streptomycin or dihydrostreptomycin, and penicillin used in making the batch for potency, toxicity, moisture, pH, streptomycin content of the dihydrostreptomycin, crystallinity if it is crystalline dihydrostreptomycin, and crystillinity and penicillin G content of the procaine penicillin G. He shall also submit in connection with his request a sample consisting of not less than 8 packages of such ointment and (unless they were previously submitted), accurately representative samples of the following, in the quantities indicated.

(1) The neomycin used in making the batch: 5 packages, each containing approximately equal portions of not less than 0.5 gram.

(2) The streptomycin or dihydrostreptomycin used in making the batch: 16 packages, each containing approximately equal portions of not less than 0.5 gram.

(3) The procaine penicillin G used in making the batch: 10 packages, each containing approximately equal portions of not less than 300 milligrams.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $6.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of neomycin, streptomycin, or dihydrostreptomycin, and penicillin.

§ 146c.224 Tetracycline hydrochloride nystatin capsules; tetracycline phosphate complex-nystatin capsules.

Tetracycline hydrochloride-nystatin capsules and tetracycline phosphate complex-nystatin capsules are capsules that conform to all the requirements and procedures prescribed by § 146c.204 for tetracycline hydrochloride capsules and tetracycline phosphate complex capsules, except that:

(a) Each capsule contains not less than 100,000 units of nystatin. The nystatin used is produced by the growth of *Streptomyces noursei*. It is a white to yellow to light-tan powder. It is very slightly soluble in water, moderately soluble in methyl alcohol, butyl alcohol, or propyl alcohol. Its potency is not less than 2,000 units per milligram. It is nontoxic. Its pH in a 3-percent aqueous suspension is not less than 6.5 and not more than 8.0. Its moisture content is not more than 5 percent. It exhibits absorption maxima, within ± 2 mμ, at 230 mμ, 291 mμ, 305 mμ, and 319 mμ when dissolved in methyl alcohol and the ratio of the absorption peak at 230 ± 2 mμ and the middle of the shoulder at 279 ± 2 mμ, A_{230}/A_{279}, is not less than 0.90 and not more than 1.25.

(b) If it is tetracycline phosphate complex-nystatin capsules, its expiration date shall be 18 months after the month during which the batch was certified, except that the date may be one of the longer dates permitted in § 146c.204 if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by this section.

(c) In addition to complying with the requirements of § 146c.204 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the nystatin used in making the batch for potency, toxicity, pH, moisture, and identity. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the nystatin used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $1.00 for each capsule.

(2) $4.00 for each immediate container of nystatin.

§ 146c.225 Tetracycline hydrochloride-nystatin tablets.

Tetracycline hydrochloride-nystatin tablets are tablets that conform to all requirements and are subject to all procedures prescribed by § 146c.224 for tetracycline hydrochloride-nystatin capsules, except that the expiration date is the date that is 24 months after the month during which the batch was certified. In addition to the requirements prescribed by § 146c.224, tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. A person who requests certification shall therefore also submit for disintegration-time studies, results of this test made by him and a sample of six tablets. The fee for the tablets submitted for disintegration-time studies shall be $3.00.

§ 146c.226 Tetracycline and vasoconstrictor suspension; tetracycline and ------ (the blank being filled in with the common or usual name of the vasoconstrictor) suspension.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline and vasoconstrictor suspension is tetracycline and a suitable vasoconstrictor, with or without one or more suitable and harmless suspending or dispersing agents, preservatives, buffer substances, colorings, and flavorings, with or without cortisone or a suitable derivative of cortisone, suspended in a suitable and harmless vehicle. Each milliliter contains a quantity of tetracycline equivalent to not less than 3.75 milligrams of tetracycline hydrochloride. The pH is not less than 3.0 nor more than 5.0. The tetracycline used conforms to the requirements of § 146c.220(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside label or container and the immediate container, as hereinafter indicated, the following:

(i) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(ii) If it contains, in addition to tetracycline, one or more other active ingredients specified in paragraph (a) of this section, after the name "tetracycline and vasoconstrictor suspension," wherever such name appears, the words "with ----------," the blank being filled in with the common or usual name of each such other ingredient used, in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the tetracycline used in making the batch was completed, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per milliliter, and pH.

(ii) The tetracycline used in making the batch: Potency, toxicity, moisture, pH, crystallinity, and absorptivity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One package for each 5,000 packages in the batch, but in no case less than 5 packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged

during the intervals are approximately equal.

(ii) The tetracycline used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.220 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams, except if cortisone, or a derivative of cortisone is used, such package shall contain approximately 100 milligrams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.227 Chlortetracycline spray dressing (chlortetracycline hydrochloride spray dressing).

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline spray dressing is chlortetracycline hydrochloride ointment and one or more suitable and harmless inert gases. It is sterile. The chlortetracycline hydrochloride ointment used conforms to the standards prescribed for chlortetracycline hydrochloride ointment by § 146c.-202(a), except that its potency is not less than 20 milligrams per gram. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not less than 30 grams of ointment and shall contain one or more suitable and harmless inert gases.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date ----------," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline used in making the batch was completed, the quantity of each ingredient used in making such batch, the date on which the latest assay of the drug comprising such batch was completed, and that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per gram, sterility, and moisture.

(ii) The chlortetracycline used in making the batch: Potency, toxicity, moisture, pH, and crystallinity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 6 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each component of the ointment base, each containing approximately 200 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i) (*a*) (ii), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.228 Chlortetracycline hydrochloride-neomycin tablets veterinary; tetracycline hydrochloride-neomycin tablets veterinary.

Chlortetracycline hydrochloride-neomycin tablets veterinary and tetracycline hydrochloride-neomycin tablets veterinary are tablets that conform to all requirements and are subject to all procedures prescribed by § 146c.204 for chlortetracycline hydrochloride capsules and tetracycline hydrochloride capsules, except that:

(a) Each tablet shall contain not less than 125 milligrams of neomycin.. The neomycin used conforms to the requirements prescribed by § 146a.410(a) (2) of this chapter. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour.

(b) [Reserved]

(c) In addition to complying with the requirements of § 146c.204(d), a person who requests certification of a batch shall submit with his request a statement showing the number of milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride and neomycin in each tablet of the batch, the batch mark, and, if required by paragraph (a) of this section, disintegration time, and (unless it was previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, toxicity, moisture, and pH. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making the batch, and a sample of 6 tablets for disintegration-time studies.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(1) $1.00 for each tablet submitted in accordance with the requirements of § 146c.204(d) (3) (i).

(2) $3.00 for all tablets submitted for disintegration-time studies in accordance with paragraph (c) of this section.

§ 146c.229 Tetracycline-nystatin oral suspension; tetracycline phosphate complex-nystatin oral suspension (tetracycline phosphate complex-nystatin oral drops).

Tetracycline-nystatin oral suspension and tetracycline phosphate complex-nystatin oral suspension are suspensions that conform to all the requirements and procedures prescribed by § 146c.222 for tetracycline oral suspension or tetracycline phosphate complex oral suspension, except that:

(a) Each milliliter contains not less than 25,000 units of nystatin. The nystatin used conforms to the standards prescribed by § 146c.224 (a).

(b) [Reserved]

(c) In addition to complying with the requirements of § 146c.222 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the nystatin used in making the batch for potency, toxicity, pH, moisture, and identity. He shall also submit in connection with his request a sample consisting of not less than six immediate containers of the batch and (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the nystatin used in making the batch.

(d) The fee for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $5.00 for each immediate container of the batch.

(2) $4.00 for each package of the nystatin used in making the batch.

§ 146c.230 Chlortetracycline hydrochloride powder topical; tetracycline hydrochloride powder topical.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline hydrochloride powder topical and tetracycline hydrochloride power topical are chlortetracycline hydrochloride or tetracycline hydrochloride, with or without suitable and harmless preservatives, diluents, and local anesthetics. The moisture content is not more than 2 percent. The chlortetracycline hydrochloride used conforms to the rerequirements of § 146c.201(a), except § 146c.201 (a) (2), (3), (4), and (5). The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a), except § 146c.218 (a) (2), (3), (4), and (5). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container may contain one or more suitable and harmless inert gases.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride per gram or per immediate container.

(iii) The statement "Expiration date ----------," the blank being filled in with one of the following dates:

(*a*) If it is chlortetracycline hydrochloride powder topical, 48 months after the month during which the batch was certified.

(*b*) If it is tetracycline hydrochloride powder topical, 24 months after the month during which the batch was certified, except that the date that is 36 months, 48 months, or 60 months after the month during which the batch was certified may be used if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by paragraph (a) of this section.

(*c*) If it is packaged with inert gases, 24 months.

(iv) If it contains preservatives or local anesthetics, the name and quantity of each such ingredient.

(2) On the circular or other labeling within or attached to the package, if it is packaged for dispensing, adequate directions and warnings for prophylactic use by man, or for the veterinary use of such drug. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other uses of such drug by practitioners licensed by law to administer it will be sent to such practitioners on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline hydrochloride or tetracycline hydrochloride used in making such batch was completed, the number of milligrams in each immediate container, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The chlortetracycline hydrochloride or tetracycline hydrochloride used in making the batch: Potency, moisture, pH, crystallinity, and absorptivity if it is tetracycline hydrochloride.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One immediate container for each 5,000 containers in the batch, but in no case less than 5 immediate containers (or if it is packaged with inert gases, not less than 7 immediate containers). Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline hydrochloride or tetracycline hydrochloride used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each, containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $ 4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.3 (d) of this chapter.

(f) *Exemption of chlortetracycline hydrochloride powder topical and tetracycline hydrochloride powder topical for veterinary use from certification.* Chlortetracycline hydrochloride powder topical and tetracycline hydrochloride powder topical that conform to the requirements of paragraphs (a), (b), and (c) of this section shall be exempt (unless they are packaged with inert gases) from the requirements of sections 502 (l) and 507 of the act, if they comply with all the following conditions:

(1) They are intended solely for veterinary use and are conspicuously so labeled.

(2) The labels bear an expiration date that is 48 months, if it is chlortetracycline hydrochloride powder topical, or 24 months, if it is tetracycline hydro-

chloride powder topical, after the month in which the batch was last assayed and released by the manufacturer, except, if it is tetracycline hydrochloride powder topical, the date that is 36 months, 48 months, or 60 months may be used if the manufacturer has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by paragraph (a) of this section.

(3) The circular or other labeling within or attached to the package bears information that the drug is intended solely for the prevention of infection in superficial cuts and abrasions and for the treatment of pinkeye in veterinary animals, and further, bears directions and warnings adequate for such use.

§ 146c.231 Capsules tetracycline and oleandomycin phosphate; capsules tetracycline and triacetyloleandomycin; capsules tetracycline hydrochloride and oleandomycin phosphate; capsules tetracycline hydrochloride and triacetyloleandomycin.

(a) *Standards of identity, strength, quality, and purity.* Capsules tetracycline and oleandomycin phosphate, capsules tetracycline and triacetyloleandomycin, capsules tetracycline hydrochloride and oleandomycin phosphate, and capsules tetracycline hydrochloride and triacetyloleandomycin are capsules that conform to all requirements and procedures prescribed by § 146c.204 for tetracycline capsules and tetracycline hydrochloride capsules, except that:

(1) Each capsule contains not less than 30 milligrams of oleandomycin activity either as the phosphate salt or as triacetyloleandomycin. The oleandomycin phosphate or the triacetyloleandomycin used is the crystalline phosphate salt or the triacetyl ester of a kind of oleandomycin, produced by the growth of Streptomyces antibioticus. If oleandomycin phosphate is used, its potency is not less than 750 μg. per milligram; it is nontoxic; its moisture content is not more than 5.0 percent; its pH in a solution containing 100 milligrams per milliliter is not less than 3.0 and not more than 6.0. If triacetyloleandomycin is used its potency is not less than 760 micrograms per milligram. It is nontoxic; its moisture content is not more than 1.0 percent; its R_f value by paper chromatography is approximately 0.85. If more than one spot appears on the paper chromatogram, determine its acetyl value, which is not less than 15.3 percent and not more than 16.0 percent; its pH in a saturated aqueous alcohol solution containing 100 milligrams per milliliter is not less than 7.0 and not more than 8.5.

(2) The moisture content of the capsule is not more than 6 percent.

(3) The expiration date of the drug shall be 24 months, except that the date that is 36 months after the month during which the batch was certified may be used if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(4) In addition to complying with the requirements of § 146c.204 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the oleandomycin phosphate or triacetyloleandomycin used in making the batch for potency, toxicity, moisture, pH, crystallinity, and R_f value and acetyl value if triacetyloleandomycin is used. He shall also submit in connection with his request (unless previously submitted) a sample consisting of 10 packages, each containing approximately equal portions or not less than 300 milligrams of the oleandomycin used in making the batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (4) of this section shall be:

(1) $4.00 for each immediate container of oleandomycin.

(2) $5.00 for each immediate container of triacetyloleandomycin.

(3) $1.00 for each capsule.

§ 146c.232 Tetracycline phosphate complex.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline phosphate complex is the crystalline sodium metaphosphate complex of a kind of tetracycline. It is so purified and dried that:

(1) Its potency is not less than 750 μg. per milligram on the anhydrous basis.

(2) It is nontoxic.

(3) Its moisture content is not more than 9 percent.

(4) Its pH in an aqueous suspension prepared by adding 10 milligrams per milliliter is not less than 2.0 and not more than 4.0.

(5) Its absorptivity at 380 mμ, calculated on the anhydrous basis, is 82.0±4.9 percent of the tetracycline hydrochloride working standard treated as described in § 141c.218(e).

(6) It does not contain any tetracycline as the hydrochloride and not more than 1 percent as tetracycline base.

(b) *Packaging; labeling; request for certification, samples; fees.* Tetracycline phosphate complex conforms to all requirements and procedures prescribed for tetracycline by § 146c.220 (b), (c), (d), and (e), except that it shall be labeled with an expiration date that is 18 months after the month during which the batch was certified, and except that the sample submitted for certification shall contain one additional package containing approximately 1 gram.

§ 146c.233 Tetracycline - oleandomycin phosphate for oral suspension.

Tetracycline-oleandomycin phosphate for oral suspension conforms to all requirements and procedures prescribed by § 146c.205 for tetracycline powder, except that:

(a) When reconstituted as directed in the labeling, each milliliter shall contain not less than 16 milligrams of tetracycline and not less than 8 milligrams of oleandomycin as the phosphate salt. The crystalline oleandomycin phosphate used conforms to the standards prescribed by § 146c.231 (a) (1).

(b) The moisture content is not more than 5 percent.

(c) The pH of the suspension when reconstituted as directed in its labeling is not less than 4.0 and not more than 7.0.

(d) The expiration date of the drug shall be 24 months.

(e) In addition to complying with § 146c.205 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the oleandomycin phosphate used in making the batch for potency, toxicity, moisture, pH, and crystallinity. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the batch and (unless previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the oleandomycin used in making the batch.

(f) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (e) of this section shall be:

(1) 5.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of the oleandomycin used in making the batch.

§ 146c.234 Capsules tetracycline hydrochloride and novobiocin; capsules tetracycline phosphate complex and novobiocin.

Capsules tetracycline hydrochloride and novobiocin and capsules tetracycline phosphate complex and novobiocin are capsules that conform to all requirements and procedures prescribed by § 146c.204 for tetracycline hydrochloride capsules and tetracycline phosphate complex capsules, except that:

(a) Unless it is intended solely for veterinary use and is conspicuously so labeled, each capsule contains not less than 62.5 milligrams of novobiocin as the monosodium salt. The crystalline novobiocin used conforms to the requirements for novobiocin prescribed by § 146a.53(a) of this chapter.

(b) If it is intended solely for veterinary use and is conspicuously so labeled it may contain cortisone or a suitable derivative of cortisone.

(c) The moisture content of the capsules is not more than 4 percent if it contains tetracycline hydrochloride and not more than 9 percent if it contains tetracycline phosphate complex.

(d) The expiration date shall be the date that is 18 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months or 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time. If it is intended solely for veterinary use and it contains cortisone

or a derivative of cortisone, in addition to the labeling prescribed by this section, its label and labeling shall conform also with the requirements of § 1.106(c) of this chapter (regulations issued under section 502(f) of the act).

(e) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (d) of this section shall be:

(1) $4.00 for each immediate container of novobiocin.

(2) $1.00 for each capsule submitted.

§ 146c.235 Tetracycline hydrochloride-oleandomycin phosphate for aqueous injection.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride-oleandomycin phosphate for aqueous injection is a dry mixture of tetracycline hydrochloride and oleandomycin phosphate with one or more suitable and harmless buffer substances. Each vial contains not less than 167 milligrams of tetracycline hydrochloride and not less than 83 milligrams of oleandomycin phosphate. It is sterile, nontoxic, nonpyrogenic, and contains no histamine or histamine-like substances; its moisture content is not more than 3.0 percent; the pH of the suspension, when reconstituted as directed in its labeling, is not less than 1.8 and not more than 3.0. The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a). The crystalline oleandomycin phosphate used conforms to the standards prescribed by § 146c.231 (a) (1) for potency and crystallinity. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The immediate containers shall be of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container may be packaged in combination with a container of a suitable and harmless diluent.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(ii) On the circular or other labeling within or attached to the package, a statement of the conditions under which solutions prepared from the drug should be stored.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the dates on which the latest assays of the tetracycline hydrochloride and oleandomycin phosphate used in making such batch were completed, the number of milligrams of tetracycline hydrochloride and the number of milligrams of oleandomycin phosphate in each package, the date on which the latest assay of the drug comprising the batch was completed, the quantity of each other ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section. If such batch or any part thereof it to be packaged with a diluent, such request shall also be accompanied by a statement that such diluent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request the results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency, sterility, toxicity, pyrogens, histamine, moisture, and pH.

(ii) The tetracycline hydrochloride used in making the batch: Potency, absorptivity, and crystallinity.

(iii) The oleandomycin phosphate used in making the batch: Potency and crystallinity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 12 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The tetracycline hydrochloride used in making the batch: 3 packages containing approximately equal portions of not less than 500 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) The oleandomycin used in making the batch: 2 packages containing approximately equal portions of not less than 500 milligrams.

(iv) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each, containing approximately 5 grams.

(v) In case of an initial request for certification of a batch that is to be packaged in combination with a diluent that is not recognized by the U. S. P. or when any change is made in the composition of such diluent: 5 packages of the diluent included in the combination.

(4) The results referred to in subparagraph (2) (ii) and (iii) of this paragraph and the samples referred to in subparagraph (3) (ii) and (iii) of this paragraph are not required if such results or samples have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (d) of this section shall be:

(1) $5.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $10.00 for all immediate containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), and (v) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 of this chapter.

§ 146c.236 Tetracycline-nystatin for oral suspension.

Tetracycline-nystatin for oral suspension conforms to all requirements and procedures prescribed by § 146c.205 for tetracycline powder, except § 146c.205 (f), and except that:

(a) When reconstituted as directed in the labeling, each milliliter shall contain not less than 25 milligrams of tetracycline and not less than 25,000 units of nystatin. The nystatin used conforms to the standards prescribed by § 146c.224 (a).

(b) The pH of the suspension, when reconstituted as directed in its labeling, is not less than 4.5 and not more than 5.5.

(c) The expiration date of the drug shall be 12 months, except that the date that is 18 months or 24 months after the month during which the batch was certified may be used if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(d) In addition to complying with the requirements of § 146c.205 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests

and assays of the nystatin used in making the batch for potency, toxicity, pH, moisture, and identity. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the nystatin used in making the batch.

(e) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (d) of this section shall be:

(1) $5.00 for each immediate container in the sample of the batch.

(2) $4.00 for each immediate container of the nystatin used in making the batch.

§ 146c.237 Chlortetracycline-neomycin-streptomycin ointment; chlortetracycline-neomycin-dihydrostreptomycin ointment; tetracycline hydrochloride-neomycin-streptomycin ointment; tetracycline hydrochloride-neomycin-dihydrostreptomycin ointment.

(a) Chlortetracycline-neomycin-streptomycin ointment, chlortetracycline-neomycin-dihydrostreptomycin ointment, tetracycline hydrochloride-neomycin-streptomycin ointment, and tetracycline hydrochloride-neomycin-dihydrostreptomycin ointment conform to all requirements and are subject to all procedures prescribed by § 146c.202 for chlortetracycline hydrochloride ointment and tetracycline hydrochloride ointment, except that:

(1) They contain not less than 28 milligrams of chlortetracycline hydrochloride or tetracycline hydrochloride per gram.

(2) They contain not less than 14 milligrams of neomycin per gram. The neomycin used conforms to the requirements prescribed by § 146e.410 (a) (2) of this chapter, except the standard for toxicity.

(3) They contain not less than 14 milligrams of streptomycin or dihydrostreptomycin per gram. The streptomycin used conforms to the standards prescribed by § 146b.101 (a) of this chapter, except § 146b.101 (a) (2), (3), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed by § 146b.103 of this chapter, except the standards for sterility, toxicity, pyrogens, and histamine.

(b) Its expiration date shall be 36 months after the month during which the batch was certified.

(c) In addition to complying with the requirements of § 146c.202 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch marks and (unless they were previously submitted) the results and dates of the latest tests and assays of the neomycin and streptomycin or dihydrostreptomycin used in making the batch for potency, moisture, pH, streptomycin content of the dihydrostreptomycin and crystallinity if it is crystalline dihydrostreptomycin. He shall also submit in connection with his request a sample consisting of not less than 8 packages of such ointment and (unless they were previously submitted) accurately representative samples of the following, in the quantities indicated:

(1) The neomycin used in making the batch: 5 packages, each containing approximately equal portions of not less than 0.5 gram.

(2) The streptomycin or dihydrostreptomycin used in making the batch; 6 packages, each containing approximately equal portions of not less than 0.5 gram.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $6.00 for each immediate container of the ointment.

(2) $4.00 for each immediate container of neomycin and streptomycin or dihydrostreptomycin.

§ 146c.238 Tablets tetracycline hydrochloride and novobiocin.

Tablets tetracycline hydrochloride and novobiocin are tablets that conform to all requirements and procedures prescribed by § 146c.204 for tetracycline hydrochloride capsules, except that:

(a) Unless they are intended solely for veterinary use and are conspicuously so labeled, each tablet shall contain not less than 125 milligrams of novobiocin as the crystalline monosodium salt or crystalline calcium salt. The novobiocin used conforms to the requirements for monosodium novobiocin prescribed by § 146a.53 (a) of this chapter, or if calcium novobiocin is used, it is produced by the growth of Streptomyces niveus, has a potency of not less than 750 μg. per milligram, is nontoxic, has a moisture content of not more than 10 percent, and its pH in a saturated aqueous solution is not less than 6.5 and not more than 8.5.

(b) The moisture content of the tablets is not more than 6 percent. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour.

(c) The expiration date of the drug shall be 36 months.

(d) In addition to complying with the requirements of § 146c.204, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, and if required by paragraph (b) of this section, disintegration time, and (unless previously submitted) the results and the date of the latest tests and assays of the novobiocin used in making the batch for potency, toxicity, pH, crystallinity, and moisture. He shall submit a sample of 6 tablets for disintegration-time studies. He shall also submit in connection with his request (unless previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the novobiocin used in making the batch.

(e) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(1) $1.00 for each tablet submitted in accordance with the requirements of § 146c.204(d) (3) (i).

(2) $3.00 for all tablets submitted for disintegration-time studies in accordance with paragraph (d) of this section.

§ 146c.239 Tetracycline-novobiocin for oral suspension.

Tetracycline-novobiocin powder for oral suspension conforms to all requirements and procedures prescribed by § 146c.205 for tetracycline powder, except paragraph (f) of that section, and except that:

(a) When prepared as directed in its labeling, each milliliter contains 12.5 milligrams of crystalline monosodium novobiocin or crystalline calcium novobiocin and a quantity of tetracycline equivalent to 12.5 milligrams of tetracycline hydrochloride. The novobiocin used conforms to the requirements prescribed by § 146a.53 (a) of this chapter or § 146c.238.

(b) Its moisture content is not more than 5 percent.

(c) [Reserved.]

(d) In addition to complying with the requirements of § 146c.205, a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the novobiocin used in making the batch for potency, toxicity, crystallinity, pH, and moisture. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the batch and (unless previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the novobiocin used in making the batch.

(e) The fees for the services rendered in accordance with the requirements of paragraph (d) of this section shall be:

(1) $5.00 for each immediate container of the batch submitted.

(2) $4.00 for each immediate container of novobiocin submitted.

§ 146c.240 Tetracycline-triacetyloleandomycin syrup (tetracycline-triacetyloleandomycin oral drops; tetracycline-triacetyloleandomycin homogenized mixture).

(a) Tetracycline - triacetyloleandomycin syrup conforms to all requirements and procedures prescribed by § 146c.217 for tetracycline syrup, except that:

(1) Each milliliter contains a quantity of triacetyloleandomycin equivalent to not less than 8.0 milligrams of oleandomycin activity, and a quantity of tetracycline equivalent to not less than 16.0 milligrams of tetracycline hydrochloride. The triacetyloleandomycin used conforms to the requirements of § 146c.231 (a) (1).

(2) It may contain glucosamine hydrochloride.

(3) Its pH is not less than 4.0 and not more than 7.0.

(4) [Reserved.]

(5) In addition to complying with § 146c.217 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the triacetyloleandomycin used in making the batch for potency, toxicity, moisture,

pH, crystallinity, R_f value, and acetyl value. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the triacetyloleandomycin used in making the batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (5) of this section shall be:

(1) $5.00 for each immediate container in the sample of the batch.

(2) $5.00 for each immediate container in the sample of triacetyloleandomycin used in making the batch.

§ 146c.241 Chlortetracycline seed.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline seed is dehulled millet seed containing chlortetracycline. It contains 0.5 milligram of chlortetracycline per gram. Its moisture content is not more than 10 percent. The chlortetracycline used conforms to the requirements prescribed therefor by § 146c.201 (a), except § 146c.201 (a) (2), (4), and (5), or to the requirements prescribed by § 146c.205 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a well closed container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of chlortetracycline in each gram of the batch.

(iii) The statement "For oral veterinary use only."

(iv) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline used in making such batch was completed, the number of milligrams in each immediate container, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The chlortetracycline used in making the batch: Potency, toxicity, moisture, pH, and crystallinity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One container for each 5,000 containers in the batch, but in no case less than five immediate containers. Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time the containers are being filled that the quantities filled during the intervals are approximately equal.

(ii) The chlortetracycline used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each, containing approximately 5 grams.

(4) The results referred to in subparagraph (2) (ii) of this paragraph and the sample referred to in subparagraph (3) (ii) of this paragraph are not required if such results or sample has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.242 Tetracycline-neomycin complex powder topical; tetracycline hydrochloride-neomycin sulfate powder topical.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline-neomycin complex powder topical is a dry powder of tetracycline-neomycin complex; tetracycline hydrochloride-neomycin sulfate powder topical is a mixture of equal parts of crystalline tetracycline hydrochloride and neomycin sulfate. Each may contain one or more suitable and harmles diluents and suspending agents. Each is sterile. The moisture content of tetracycline-neomycin complex powder topical is not more than 7.5 percent. The moisture content of tetracycline hydrochloride-neomycin sulfate powder topical is not more than 2.0 percent. The tetracycline hydrochloride used conforms to the requirements of § 146c.218(a). The neomycin sulfate used conforms to the standards prescribed by § 146e.410(a) (2) of this chapter. The water-soluble, acetone-insoluble tetracycline-neomycin complex used contains the equivalent of 400 milligrams of tetracycline hydrochloride and 400 milligrams of neomycin base per gram. It is nontoxic, has a moisture content of not more than 7.5 percent, and its pH in a 1 percent aqueous solution is not less than 7.5 and not more than 9.0. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification; samples; fees.* (1) In addition to complying with the requirements of § 146c.230 (b) and (c), each package shall bear on its label and labeling the number of milligrams of neomycin per gram or per immediate container. The expiration date of the drug shall be 12 months.

(2) In addition to complying with § 146c.230(d), a person who requests certification of a batch of tetracycline-neomycin complex powder topical shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the tetracycline-neomycin complex used in making the batch for potency, toxicity, moisture, and pH. He shall also submit in connection with his request a sample consisting of 10 immediate containers of the batch for sterility testing. He shall also submit in connection with his request (unless previously submitted) a sample consisting of 10 packages each containing not less than 60 milligrams of the tetracycline-neomycin complex used in making the batch. In addition to complying with § 146c.230(d), a person who requests certification of a batch

of tetracycline hydrochloride-neomycin sulfate powder topical shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and the date of the latest tests and assays of the neomycin sulfate used in making the batch for potency, toxicity, moisture, and pH and for the tetracycline hydrochloride used he shall submit his results for toxicity. He shall also submit in connection with his request a sample consisting of 10 immediate containers of the batch for sterility testing, and (unless previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin sulfate used in making the batch.

(3) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(i) $10.00 for all immediate containers submitted for sterility testing.

(ii) $5.00 for each immediate container of the batch.

(iii) $5.00 for each immediate container of tetracycline-neomycin complex used in making the batch.

(iv) $4.00 for each immediate container of neomycin sulfate used in making the batch of tetracycline hydrochloride-neomycin sulfate powder topical.

§ 146c.243 Capsules tetracycline hydrochloride - triacetyloleandomycin - nystatin.

Capsules tetracycline hydrochloride-triacetyloleandomycin-nystatin conform to all requirements and procedures prescribed by § 146c.231 for tetracycline hydrochloride and triacetyloleandomycin capsules, except that:

(a) Each capsule contains not less than 125,000 units of nystatin. The nystatin used conforms to the standards prescribed by § 146c.224 (a).

(b) The expiration date of the drug shall be 18 months.

(c) In addition to complying with the requirements of § 146c.231 (a) (4), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the nystatin used in making the batch for potency, toxicity, pH, moisture, and identity. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the nystatin used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $1.25 for each capsule.

(2) $4.00 for each immediate container of nystatin.

§ 146c.244 Tetracycline hydrochloride-neomycin spray ointment topical.

(a) *Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride-neomycin spray ointment topical is tetracycline hydrochloride and neomycin in a suitable and harmless ointment base and one or more suitable and harmless inert gases. Each gram of ointment contains not less than 15 milligrams of tetracycline hydrochloride and not less than 15 milligrams of neomycin. It is sterile. Its moisture content is not more than 3.0 percent. The tetracycline hydrochloride used conforms to the requirements of § 146c.218 (a), except §146c.218 (a) (1), (2), (3), (4), and (5), but its potency is not less than 720 μg. per milligram. The neomycin used conforms to the standards prescribed by § 146e.410 (a) (2) of this chapter for potency, moisture, and pH. Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not less than 30 grams of ointment and shall contain one or more suitable and harmless inert gases.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates on which the latest assays of the tetracycline hydrochloride and neomycin used in making such batch were completed, the quantity of each ingredient used in making such batch, the date on which the latest assay of the drug comprising such batch was completed, and that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: The number of milligrams of tetracycline hydrochloride and the number of milligrams of neomycin per gram; sterility; moisture.

(ii) The tetracycline hydrochloride and neomycin used in making the batch: Potency, moisture, pH, crystallinity.

(3) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: One immediate container for each 5,000 immediate containers in the batch, but in no case less than six immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The tetracycline hydrochloride used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.218 (b).

(iii) The neomycin used in making the batch: Five packages, each containing approximately equal portions of not less than 0.5 gram.

(iv) In case of an initial request for certification, each other ingredient used in making the batch: One package of each component of the ointment base, each containing approximately 200 grams.

(4) The results referred to in subparagraph (2) (ii) of this paragraph and the samples referred to in subparagraph (3) (ii) and (iii) of this paragraph are not required if such results or samples have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $5.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $10.00 for all immediate containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146c.245 Tetracycline-triacetyloleandomycin for oral suspension.

Tetracycline - triacetyloleandomycin for oral suspension conforms to all requirements and procedures prescribed by § 146c.240 for tetracycline-triacetyloleandomycin syrup, except that:

(a) It is a dry powder which, when reconstituted with a diluent as directed in its labeling, conforms to the standards prescribed for tetracycline-triacetyloleandomycin syrup.

(b) Its moisture content is not more than 5 percent.

§ 146c.246 Tetracycline hydrochloride-neomycin in oil suspension.

(a) Tetracycline hydrochloride-neomycin in oil suspension conforms to all requirements and is subject to all procedures prescribed by § 146c.202 for tetracycline hydrochloride ointment, except that:

(1) It contains not less than 10 milligrams of neomycin per milliliter. The neomycin used conforms to the requirements prescribed by § 146e.410(a)(2) of this chapter, except the standard for toxicity.

(2) If it is intended solely for veterinary use, it may contain one or more suitable fungicides and miticides. If it contains such ingredients, the labeling shall bear the name and quantity of each contained in each milliliter.

(3) Its labeling shall also show the quantity of neomycin contained in each milliliter.

(b) In addition to complying with the requirements of § 146c.202(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and, unless it was previously submitted, the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, moisture, and pH. He shall also submit in connection with his request a sample consisting of not less than 6 packages of such drug and, unless it was previously submitted, a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram of the neomycin used in making such batch.

(c) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(1) $5.00 for each immediate container of the oil.

(2) $4.00 for each sample of neomycin.

§ 146c.247 Chlortetracycline hydrochloride impregnated surgical silk.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline hydrochloride impregnated surgical silk is surgical silk that is impregnated with crystalline chlortetracycline hydrochloride. Its content of chlortetracycline hydrochloride is not less than 1.5 percent of the total weight of the suture. It is sterile. Its moisture content is not more than 4 percent. The chlortetracycline hydrochloride used conforms to the standards prescribed by § 146c.201(a), except § 146c.201(a) (2), (4), and (5). The surgical silk used conforms to the standards prescribed therefor by the U.S.P. for nonabsorbable surgical sutures.

(b) *Packaging.* The sutures shall be packaged in tight containers as defined by the U.S.P. The immediate containers shall be so sealed that the contents cannot be used without destroying the seal and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each immediate container may contain a suitable sterile surgical needle.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of milligrams of chlortetracycline hydrochloride per suture.

(iii) The length, size, and type of silk contained in the package.

(iv) The statement "Expiration date ----------," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(v) The statement "Caution: Federal law prohibits dispensing without prescription."

(2) [Reserved]

(3) On the circular or other labeling within or attached to the package, if it is packaged for dispensing, adequate directions and warnings for its use by practitioners licensed by law to administer such drug.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline hydrochloride used in making such batch was completed, the potency of each gram of the surgical silk, the date on which the latest assay of the batch was completed, and a statement that the surgical silk used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per suture, moisture, and sterility.

(ii) The chlortetracycline hydrochloride used in making the batch: Potency, toxicity, moisture, pH, and crystallinity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: 1 package for each 5,000 packages in the batch, but in no case less than 20 packages.

(*b*) For sterility testing: 10 packages.

Such samples shall be collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline used in making the batch: 10 packages, each containing approximately equal portions of not less than 60 milligrams, packaged in accordance with the requirements of § 146c.201(b).

(iii) In case of an initial request for certification: 1 package consisting of approximately 1.0 gram of the surgical silk used.

(4) The result referred to in subparagraph (2)(ii) of this paragraph and the sample referred to in subparagraph (3)(ii) of this paragraph are not required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $1.50 for each package in the sample submitted in accordance with paragraph (d)(3)(i)(*a*); $4.00 for each package in the samples submitted in accordance with paragraph (d)(3)(ii) and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d)(3)(i)(*b*) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.248 Rolitetracycline.

(a) *Standards of identity, strength, quality, and purity.* Rolitetracycline is the crystalline *N*-(pyrrolidinomethyl) derivative of a kind of tetracycline. It is so purified and dried that:

(1) Its potency is not less than 900 μg. per milligram on the anhydrous basis.

(2) It is nontoxic.

(3) Its moisture content is not more than 3.0 percent.

(4) Its pH is an aqueous solution prepared by adding 10 milligrams per milliliter is not less than 7.0 and not more than 9.0, and such solution is substantially clear.

(5) Its absorptivity at 380 mμ is 100±4.4 percent of the rolitetracycline working standard similarly treated, both calculated on the anhydrous basis.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U.S.P., and shall be of such composition as will not cause any change in the strength,

quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of rolitetracycline shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of micrograms of rolitetracycline per milligram and the total number of grams in the immediate container.

(3) The statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which it was certified, except that the blank may be filled in with the date that is 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed in paragraph (a) of this section.

(4) The statement "Caution: Federal law prohibits dispensing without prescription."

(5) The statement "For manufacturing use only."

(6) The statement "Not sterile."

(d) *Request for certification, check tests, and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, crystallinity, absorptivity, and identity.

(2) Such person shall submit with his request an accurately representative sample of the batch consisting of 10 packages, each containing approximately 250 milligrams taken from a different part of such batch, and each packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which rolitetracycline is to be used, the manufacturer of the batch that is to be so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed in subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer the results of such check tests and assays as are so requested.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) and (3) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.249 Rolitetracycline for intravenous use.

(a) *Standards of identity, strength, quality, and purity.* Rolitetracycline for intravenous use is a dry mixture of rolitetracycline and one or more suitable buffer substances. It is sterile. It is nontoxic. It is nonpyrogenic. It contains no histamine nor histamine-like substances. Its moisture content is not more than 5 percent. Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.0 and not more than 4.5. The rolitetracycline used conforms to the requirements of § 146c.248(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U.S.P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The immediate containers shall be of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container shall contain not less than 100 milligrams of rolitetracycline, and each may be packaged in combination with a container of a suitable and harmless diluent.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106 (b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) On the circular or other labeling within or attached to the package, a statement of the conditions under which solutions prepared from the drug should be stored and the statement "Use within 6 hours after reconstitution."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the rolitetracycline used in making such batch was completed, the number of milligrams of rolitetracycline in each package, the date on which the latest assay of the drug comprising the batch was completed, the quantity of each other ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section. If such batch or any part thereof is to be packaged with a diluent, such request shall also be accompanied by a statement that such diluent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request the results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency, sterility, toxicity, pyrogens, histamine, moisture, pH.

(ii) The rolitetracycline used in making the batch: Potency, absorptivity, crystallinity, and identity.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: One immediate container for each 5,000 immediate containers in the batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The rolitetracycline used in making the batch: 10 packages containing approximately equal portions of not less than 250 milligrams, packaged in accordance with the requirements of § 146c.248(b).

(iii) In case of an initial request for certification, each other ingredient used

in making the batch: One package of each, containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch that is to be packaged in combination with a diluent that is not recognized by the U.S.P. or when any change is made in the composition of such diluent: Five packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility: 10 packages, each containing approximately 0.25 gram.

(ii) For sterility testing: 10 packages, each containing approximately 40 milligrams of rolitetracycline.

Each such package shall be packaged in accordance with the requirements of paragraph (b) of this section.

(5) The result referred to in subparagraph (2) (ii) of this paragraph and the sample referred to in subparagraph (3) (ii) of this paragraph are not required if such result and sample have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), (iii), (iv), and 4(i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (4) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.250 Rolitetracycline for intramuscular use.

(a) *Standards of identity, strength, quality, and purity.* Rolitetracycline for intramuscular use is a dry mixture of rolitetracycline and one or more suitable buffer substances and anesthetic agents. It is sterile. It is nonpyrogenic. Its moisture content is not more than 5 percent. Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.0 and not more than 4.5. The rolitetracycline used conforms to the requirements of § 146c.248 and it contains no histamine nor histamine-like substances. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U.S.P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The immediate containers shall be of colorless transparent class, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container shall contain not less than 100 milligrams of rolitetracycline, and each may be packaged in combination with a container of a suitable and harmless diluent.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) On the circular or other labeling within or attached to the package, a statement of the conditions under which solutions prepared from the drug should be stored and the statement "Use within 6 hours after reconstitution."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the rolitetracycline used in making such batch was completed, the number of milligrams of rolitetracycline in each package, the date on which the latest assay of the drug comprising the batch was completed, the quantity of each other ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section. If such batch or any part thereof is to be packaged with a diluent, such request shall also be accompanied by a statement that such diluent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (5) of this paragraph, such person shall submit in connection with his request the results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency, sterility, pyrogens, moisture, pH.

(ii) The rolitetracycline used in making the batch: Potency, toxicity, histamine, absorptivity, crystallinity, and identity.

(3) Except as otherwise provided by subparagraph (5) of this paragraph, if such batch is packaged for dispensing, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility: One immediate container for each 5,000 immediate containers in the batch, but in no case less than 10 immediate containers.

(*b*) For sterility testing: 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The rolitetracycline used in making the batch: 10 packages containing approximately equal portions of not less than 250 milligrams, packaged in accordance with the requirements of § 146c.248(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each, containing approximately 5 grams.

(iv) In case of an initial request for the certification of a batch which is to be packaged in combination with a diluent that is not recognized by the U.S.P. or when any change is made in the composition of such diluent: Five packages of the diluent included in the combination.

(4) If such batch is packaged for repacking, such person shall submit with his request a sample consisting of the following:

(i) For all tests except sterility: 10 packages, each containing approximately 0.25 gram.

(ii) For sterility testing: 10 packages, each containing approximately 40 milligrams of rolitetracycline.

Each such package shall be packaged in accordance with the requirements of paragragh (b) of this section.

(5) The result referred to in subparagraph (2) (ii) of this paragraph and the sample referred to in subparagraph (3) (ii) of this paragraph are not required if such result and sample have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), (iii), (iv), and (4) (i) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) and (4) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination

of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.251 Demethylchlortetracycline hydrochloride.

(a) *Standards of identity, strength, quality, and purity.* Demethylchlortetracycline hydrochloride is the crystalline hydrochloride salt of the 6-demethyl homolog of chlortetracycline or a mixture of two or more such salts. It is so purified and dried that:

(1) Its potentcy is not les than 900 μg. per milligram on the anhydrous basis.

(2) It is nontoxic.

(3) Its moisture content is not more than 2.0 percent.

(4) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2.0 and not more than 3.0.

(5) Its absorptivity at 385 mμ is 100±4.2 percent of the demethylchlortetracycline hydrochloride working standard similarly treated, both calculated on the anhydrous basis.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U.S.P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of demethylchlortetracycline shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of micrograms of demethylchlortetracycline per milligram and the total number of grams in the immediate container.

(3) The statement "Expiration date _____," the blank being filled in with the date that is 36 months after the month during which it was certified.

(4) The statement "For use only in the manufacture of nonparenteral drugs."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, crystallinity, absorptivity, and identity.

(2) Such person shall submit with his request an accurately representative sample of the batch consisting of 10 packages, each containing approximately 250 milligrams taken from a different part of such batch and each packaged in accordance with the requirements of paragraph (b) of this section.

(3) In connection with contemplated requests for certification of batches of another drug in the manufacture of which demethylchlortetracycline is to be used, the manufacturer of the batch that is to be so used may request the Commissioner to make check tests and assays on a sample of such batch taken as prescribed by subparagraph (2) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer the results of such check tests and assays as are so requested.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) and (3) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.252 Capsules demethylchlortetracycline hydrochloride.

(a) *Standards of identity, strength, quality, and purity.* Capsules demethylchlortetracycline hydrochloride are capsules composed of crystalline demethylchlortetracycline hydrochloride, with or without one or more suitable and harmless buffer substances, vegetable oils, preservatives, diluents, binders, lubricants, colorings, and flavorings, enclosed in a gelatin capsule. Each capsule shall contain not less than 50 milligrams of demethylchlortetracycline hydrochloride, except if it is intended for veterinary use each capsule shall contain not less than 25 milligrams. Its moisture content is not more than 2.0 percent. The demethylchlortetracycline hydrochloride used conforms to the requirements prescribed by § 146c.251(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each capsule is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U.S.P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the capsules by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *If it is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 36 months after the month during which the batch was certified.

(2) *If it is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement, "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the demethylchlortetracycline hydrochloride used in making such batch was completed, the number of milligrams in each capsule, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per capsule and average moisture.

(ii) The demethylchlortetracycline hydrochloride used in making the batch: Potency, toxicity, moisture, pH, crystallinity, absorptivity, and identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One capsule for each 5,000 capsules in the batch, but in no case less than 30 capsules, collected by

taking single capsules at such intervals throughout the entire time of preparation that the quantities encapsulated during the intervals are approximately equal.

(ii) The demethylchlortetracycline hydrochloride used in making the batch: 10 packages, each containing approximately equal portions of not less than 250 milligrams, packaged in accordance with the requirements of § 146c.251(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) The result referred to in subparagraph (2)(ii) of this paragraph and the sample referred to in subparagraph (3)(ii) of this paragraph are not required if such result and sample have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $0.75 for each capsule in the sample submitted in accordance with paragraph (d)(3)(i) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d)(3)(ii) and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such capsules and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d).

§ 146c.253 Demethylchlortetracycline.

(a) *Standards of identity, strength, quality, and purity.* Demethylchlortetracycline is the hydrated or anhydrous crystalline compound of the 6-demethyl homolog of chlortetracycline or a mixture of two or more such compounds. It is so purified and dried that:

(1) Its potency is not less than 970 micrograms per milligram on the anhydrous basis.

(2) It is nontoxic.

(3) Its moisture content is not more than 7.5 percent.

(4) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.0 and not more than 5.5.

(5) Its absorptivity at 380 mμ, calculated on the anhydrous basis, is 107.4 ±3.88 percent of the demethylchlortetracycline hydrochloride working standard treated as described in § 141c.218(e).

(b) *Packaging; labeling; request for certification, check tests and assays, samples; fees.* Demethylchlortetracycline conforms to all requirements and procedures prescribed for demethylchlortetracycline hydrochloride by § 146c.251 (b), (c), (d), and (e).

§ 146c.254 Demethylchlortetracycline for oral suspension.

(a) *Standards of identity, strength, quality, and purity.* Demethylchlortetracycline for oral suspension is crystalline demethylchlortetracycline with or without suitable and harmless buffer substances, preservatives, diluents, colorings, and flavorings. When the suspension is prepared as directed in its labeling, each milliliter contains a quantity of demethylchlortetracycline equivalent to not less than 15 milligrams of demethylchlortetracycline hydrochloride. Its moisture content is not more than 5 percent. The demethylchlortetracycline used conforms to the requirements of § 146c.251(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the demethylchlortetracycline used in making such batch was completed, the number of milligrams in each immediate container, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The demethylchlortetracycline used in making the batch: Potency, toxicity, moisture, pH, crystallinity, absorptivity, and identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One immediate container for each 5,000 containers in the batch, but in no case less than 5 immediate containers, unless each such container is packaged to contain more than 1.0 gram, in which case the sample shall consist of 1.0 gram for each 5,000 immediate containers in the batch, but in no case less than five 1.0-gram portions.

Such samples shall be collected by taking single immediate containers or 1.0-gram portions at such intervals throughout the entire time the containers are being filled that the quantities filled during the intervals are approximately equal.

(ii) The demethylchlortetracycline used in making the batch: 10 packages, each containing approximately equal portions of not less than 250 milligrams, packaged in accordance with the requirements of § 146c.251(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) The result referred to in subparagraph (2)(ii) of this paragraph and the sample referred to in subparagraph (3)(ii) of this paragraph, are not required if such result or sample has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d)(3)(i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.255 Demethylchlortetracycline syrup (demethylchlortetracycline oral drops).

(a) Demethylchlortetracycline syrup is a syrup that contains demethylchlortetracycline with or without one or more suitable and harmless buffer substances, suspending and stabilizing agents, and preservatives, suspended in a suitable and harmless vehicle. Each milliliter contains a quantity of demethylchlortetracycline equivalent to not less than 15 milligrams of demethylchlortetracycline hydrochloride. The pH is not less than 4.0 and not more than 5.5. The crystalline demethylchlortetracycline used conforms to the requirements of § 146c.251(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P. and shall

be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the demethylchlortetracycline used in making such batch was completed, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per milliliter, pH.

(ii) The demethylchlortetracycline used in making the batch: Potency, toxicity, moisture, pH, crystallinity, absorptivity, and identity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One package for each 5,000 packages in the batch, but in no case less than 5 packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The demethylchlortetracycline used in making the batch: 10 packages each containing approximately equal portions of not less than 250 milligrams, packaged in accordance with the requirements of § 146c.251(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) The result referred to in subparagraph (2)(ii) of this paragraph and the sample referred to in subparagraph (3)(ii) of this paragraph, are not required if such result or sample has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d)(3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fees prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fees are covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.256 Chlortetracycline hydrochloride in oil oral veterinary.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline hydrochloride in oil oral veterinary is crystalline chlortetracycline hydrochloride in a suitable and harmless vegetable oil base. It contains not less than 50 milligrams of chlortetracycline hydrochloride per milliliter. Its moisture content is not more than 1.0 percent. The chlortetracycline hydrochloride used conforms to the requirements of § 146c.201(a), except § 146c.201(a) (2), (4), and (5). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate containers shall be well closed or tight containers as defined by the U.S.P. They shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good marketing, storage, and distribution practice shall be disregarded. Unless it is packaged for repacking, each such container shall be filled with a volume of chlortetracycline hydrochloride in oil in excess of that designated, which excess shall be sufficient to permit the withdrawal and the administration of the volume indicated, whether administered in single or multiple doses.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated:

(1) On the outside wrapper or container and the immediate container of the package:

(i) The batch mark.

(ii) The number of milligrams of chlortetracycline hydrochloride per milliliter.

(iii) The statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(iv) The statement "For oral use in suckling pigs only."

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chlortetracycline hydrochloride used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug was completed, and a statement that each component of the oil base used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The chlortetracycline hydrochloride used in making the batch: Potency, toxicity, moisture, pH, and crystallinity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 package for each 5,000 packages in the batch, but in no case less than 5 packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chlortetracycline used in making the batch: 10 packages, containing approximately equal portions of not less than 60 milligrams each, packaged in accordance with the requirements of § 146c.201(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: 1 package of each component of the oil base, each containing approximately 200 grams.

(4) No result referred to in subparagraph (2)(ii) of this paragraph, and no sample referred to in subparagraph (3)(ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch of the drug under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d)(3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to

determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.257 Tetracycline-amphotericin B for oral syrup; tetracycline-amphotericin B for oral drops.

Tetracycline-amphotericin B for oral syrup and tetracycline-amphotericin B for oral drops conform to all requirements and procedures prescribed by § 146c.205 for tetracycline powder, except § 146c.205(f) and except that:

(a) When reconstituted as directed in the labeling, each milliliter of the oral syrup shall contain a quantity of tetracycline equivalent to not less than 25 milligrams of tetracycline hydrochloride and not less than 5 milligrams of amphotericin B; and each milliliter of the oral drops shall contain a quantity of tetracycline equivalent to not less than 100 milligrams of tetracycline hydrochloride and not less than 20 milligrams of amphotericin B. The amphotericin B used is produced by the growth of Streptomyces nodosus. It is a yellow to orange powder. It is insoluble in water (neutral pH), anhydrous alcohols, esters, ethers, benzene, and toluene. It is soluble in dimethylformamide and dimethyl sulfoxide. Its potency is not less than 750 μg. per milligram on an anhydrous basis. It contains not more than 15 percent of amphotericin A. It is nontoxic. Its pH in a 3 percent aqueous suspension is not less than 6.0 and not more than 8.0. Its moisture content is not more than 5 percent. It exhibits absorption maxima at 362, 381, and 405 mμ when dissolved in dimethyl sulfoxide and diluted with absolute methanol.

(b) Its moisture content is not more than 2.5 percent.

(c) The expiration date shall be 18 months, except that it may be 24 months if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(d) In addition to complying with the requirements of § 146c.205(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and date of the latest tests and assays of the amphotericin B used in making the batch for potency, toxicity, pH, moisture, identity, and amphotericin A content. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the amphotericin B used in making the batch.

(e) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (d) of this section shall be:

(1) $5.00 for each immediate container in the sample of the batch.

(2) $4.00 for each immediate container of the amphotericin B used in making the batch.

§ 146c.258 Demethylchlortetracycline hydrochloride ointment.

Demethylchlortetracycline hydrochloride ointment is an ointment that conforms to all the requirements and is subject to all procedures prescribed by § 146c.202 for chlortetracycline hydrochloride ointment, except:

(a) It contains demethylchlortetracycline hydrochloride in lieu of chlortetracycline hydrochloride. The demethylchlortetracycline hydrochloride used conforms to the requirements of § 146c.251(a) except § 146c.251(a)(2). A person who requests certification of a batch of ointment shall submit in connection with his request the following results of his tests and assays made on the demethylchlortetracycline hydrochloride used in making the batch: Potency, moisture, pH, crystallinity, absorptivity, and identity.

(b) The labeling shall comply with the requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act). Its expiration date shall be 18 months after the month during which the batch was certified.

§ 146c.259 Demethylchlortetracycline hydrochloride-nystatin capsules.

Demethylchlortetracycline hydrochloride-nystatin capsules are capsules that conform to all requirements and are subject to all procedures prescribed by § 146c.252 for capsules demethylchlortetracycline hydrochloride, except that:

(a) Each capsule contains not less than 250,000 units of nystatin. The nystatin used conforms to the requirements prescribed therefor by § 146c.222 (a).

(b) The average moisture content of the capsules is not more than 5.0 percent.

(c) Its expiration date shall be the date that is 18 months after the month during which the batch was certified.

(d) In addition to complying with the requirements of § 146c.252(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the nystatin used in making the batch for potency, toxicity, pH, moisture, and identity. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the nystatin used in making the batch.

(e) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $1.00 for each capsule.

(2) $4.00 for each immediate container of nystatin.

§ 146c.260 Capsules tetracycline phosphate complex-amphotericin B.

Tetracycline phosphate complex-amphotericin B capsules are capsules that conform to all the requirements and procedures prescribed by § 146c.204 for tetracycline phosphate complex capsules, except that:

(a) Each capsule contains not less than 25 milligrams of amphotericin B. The amphotericin B used conforms to the requirements prescribed for amphotericin B by § 146c.257(a).

(b) Its moisture content is not more than 6.3 percent.

(c) *Labeling.* The expiration date of the drug shall be 12 months, except that the date that is 18 months after the month during which the batch was certified may be used if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(d) In addition to complying with the requirements of § 146c.204(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and date of the latest tests and assays of the amphotericin B used in making the batch for potency, toxicity, pH, moisture, identity, and amphotericin A content. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the amphotericin B used in making the batch.

(e) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (d) of this section shall be:

(1) $1.00 for each capsule.

(2) $4.00 for each immediate container of the amphotericin B used in making the batch.

§ 146c.261 Tetracycline-novobiocin oral suspension (tetracycline-novobiocin oral drops; tetracycline-novobiocin syrup).

Tetracycline-novobiocin oral suspension is a suspension of tetracycline and calcium novobiocin which conforms to all requirements and procedures prescribed by § 146c.239 for tetracycline-calcium novobiocin for oral suspension when the dry powder is prepared as directed in its labeling, except § 146c.239 (b), and except that:

(a) Each milliliter contains 12.5 milligrams of crystalline calcium novobiocin and a quantity of tetracycline equivalent to 12.5 milligrams of tetracycline hydrochloride; or it contains 62.5 milligrams of crystalline calcium novobiocin and a quantity of tetracycline equivalent to 62.5 milligrams of tetracycline hydrochloride.

(b) The pH is not less than 6.0 nor more than 7.0.

(c) The expiration date is 18 months after the month during which the batch was certified.

§ 146c.262 Tetracycline-amphotericin B syrup; tetracycline-amphotericin B oral drops.

Tetracycline-amphotericin B syrup and tetracycline-amphotericin B oral drops conform to all requirements and procedures prescribed by § 146c.257 for

tetracycline-amphotericin B for oral syrup and tetracycline-amphotericin B for oral drops that have been reconstituted as directed in the labeling, except § 146c.257(b), and except that:

(a) Its pH is not less than 4.0 nor more than 5.0.

(b) The expiration date of the drug shall be 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drugs as prepared by him is stable for such period of time.

§ 146c.263 Demethylchlortetracycline-nystatin for oral suspension.

Demethylchlortetracycline-nystatin for oral suspension conforms to all requirements and procedures prescribed by § 146c.254 for demethylchlortetracycline for oral suspension, except that:

(a) When reconstituted as directed in the labeling, each milliliter of oral suspension shall contain a quantity of demethylchlortetracycline hydrochloride equivalent to not less than 15 milligrams of demethylchlortetracycline hydrochloride and not less than 25,000 units of nystatin. The nystatin used conforms to the standards prescribed therefor by § 146c.224(a).

(b) The expiration date of the drug shall be 12 months.

(c) In addition to complying with the requirements of § 146c.254(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the nystatin used in making the batch for potency, toxicity, pH, moisture, and identity. He shall submit in connection with his request a sample consisting of one package for each 5,000 packages in the batch, but in no case less than 6 packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal, and (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 300 milligrams of the nystatin used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $5.00 for each immediate container in the sample of the batch.

(2) $4.00 for each immediate container of the nystatin used in making the batch.

§ 146c.264 Chlortetracycline bisulfate.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline bisulphate is the crystalline acid sulfate salt of chlortetracycline, containing butyl alcohol bound to or complexed with it. It is so purified and dried that:

(1) Its potency is equivalent to not less than 760 micrograms of chlortetracycline hydrochloride per milligram when corrected for the moisture and butyl alcohol content.

(2) It is nontoxic.

(3) Its moisture content is not more than 2.0 percent.

(4) Its butyl alcohol content is not more than 15 percent.

(5) Its sulfate content is not less than 15 percent when corrected for moisture and butyl alcohol content.

(6) Its absorptivity, when corrected for its moisture and butyl alcohol content, is 89 percent ±6 percent of that of the chlortetracycline hydrochloride working standard similarly treated and calculated on the anhydrous basis.

(b) *Packaging.* In all cases, the immediate containers shall be tight containers as defined by the U.S.P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its outside wrapper or container and the immediate container:

(1) The batch mark.

(2) The number of milligrams of chlortetracycline hydrochloride equivalent per gram and the number of grams in the immediate container.

(3) The statement "Expiration date ----------," the blank being filled in with the date that is 48 months after the month during which the batch was certified.

(4) The statement "For use only in the manufacture of nonsterile veterinary drugs."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of milligrams of chlortetracycline hydrochloride equivalent per gram, and the total number of grams in each package. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, butyl alcohol content, sulfate content, absorptivity, and crystallinity.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of 10 packages each containing approximately 0.5 gram taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146c.265 Chlortetracycline bisulfate soluble powder veterinary.

(a) *Standards of identity, strength, quality, and purity.* Chlortetracycline bisulfate soluble powder veterinary is chlortetracycline bisulfate with or without one or more suitable and harmless colorings, buffer substances, and diluents. It contains the equivalent of 25.6 grams or 102.4 grams of chlortetracycline hydrochloride per pound of powder. The moisture content is not more than 2 percent. The chlortetracycline bisulfate used conforms to the requirements of § 146c.264. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases, the immediate container shall be a tight container as defined by the U.S.P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of grams of chlortetracycline hydrochloride equivalent per pound in the immediate container.

(iii) The number of pounds of powder in each immediate container.

(iv) A statement to the effect that it is to be administered only in the drinking water of poultry, and that it should not be given to laying chickens.

(v) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification: samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the

date on which the latest assay of the chlortetracycline bisulfate used in making such batch was completed, the number of grams of chlortetracycline hydrochloride equivalent per pound, the number of pounds of powder, the number of packages of each size in the batch, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency and moisture.

(ii) The chlortetracycline bisulfate used in making the batch: Potency, toxicity, moisture, butyl alcohol content, sulfate content, absorptivity, and crystallinity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One 1-ounce portion for each 5,000 immediate containers in the batch, but in no case less than five 1-ounce portions. Such sample shall be collected by taking single 1-ounce portions at such intervals throughout the entire time the containers are being filled that the quantities filled during the intervals are approximately equal.

(ii) The chlortetracycline bisulfate used in making the batch: 10 packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146c.264(b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) The result referred to in subparagraph (2)(ii) of this paragraph, and the sample referred to in subparagraph (3)(ii) of this paragraph are not required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d)(3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

PART 146d—CERTIFICATION OF CHLORAMPHENICOL AND CHLORAMPHENICOL - CONTAINING DRUGS

Sec.

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146d.303 Chloramphenicol ointment (chloramphenicol cream).
146d.304 Chloramphenicol ophthalmic.
146d.305 Chloramphenicol palmitate.
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146d.308 Chloramphenicol otic; chloramphenicol topical.
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146d.312 Chloramphenicol-neomycin ointment.
146d.313 Chloramphenicol-polymyxin ointment.
146d.314 Chloramphenicol sodium succinate.
146d.315 Chloramphenicol sodium succinate for aqueous injection.
146d.316 Chloramphenicol — paramomycin ointment.

AUTHORITY: §§ 146d.301 to 146d.316 issued under sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 146d.301 Chloramphenicol.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol is a white to grayish-white or yellowish-white crystalline powder, occurring as needles or elongated plates. It is neutral, slightly soluble in water, but freely soluble in alcohol. It has the chemical formula D-(−)-*threo*-1-*p*-nitrophenyl-2-dichloracetamido-1,3-propanediol. It is so purified and dried that:

(1) Its potency is not less than 900 micrograms per milligram;

(2) It is sterile;

(3) It is nontoxic;

(4) It is nonpyrogenic;

(5) It contains no histamine nor histamine-like substances;

(6) Its pH in saturated aqueous solution is not less than 4.5 and not more than 7.5;

(7) Its specific rotation in absolute ethanol at 20° C. is +20°±1.5°, and at 25° C. is +18.5°±1.5°;

(8) Its melting point is 151° C. ±2°;

(9) Its absorptivity at 278 mμ does not vary more than ±3 percent from that of the chloramphenicol working standard, similarly treated.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness; each such container shall contain not more than 1.0 gm., and each may be packaged in combination with a suitable and harmless diluent.

(c) *Labeling*—(1) *If it is packaged for dispensing and it is intended for use by man.* In addition to the labeling prescribed by § 1.106(b) of this chapter, issued pursuant to section 502(f) of the act, each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement, "Warning—Blood dyscrasias may be associated with the use of chloramphenicol. It is essential that adequate blood studies be made. (See enclosed warnings and precautions)."

(*b*) The statement "Expiration date _____," the blank being filled in with the date which is 60 months after the month during which the batch was certified: *Provided, however,* That such expiration date may be omitted from the immediate container if it contains a single dose and it is packaged in an individual wrapper or container.

(ii) The circular or other labeling within or attached to the package bearing directions, precautions, and warnings for its use by physicians shall begin with the following statements, which shall be underscored or italicized:

(*a*) "Warning—Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms that are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective; or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat; or as a prophylactic agent."

(*b*) "Precautions—It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia."

(2) *If it is packaged for dispensing and it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements of subparagraph (1) of this paragraph except subdivisions (i)(*a*) and (ii); and in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions, precau-

tions, and warnings adequate for the veterinary use of the drug by the laity.

(3) *If it is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The number of micrograms of chloramphenicol per milligram or per gram and the number of grams or kilograms in the immediate container.

(ii) The batch mark.

(iii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iv) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(v) The expiration date required by subparagraph (1)(i)(*b*) of this paragraph.

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chloramphenicol shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of grams in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, histamine, pH, specific rotation, melting point, and absorptivity. If such batch or any part thereof is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) If such batch is packaged for dispensing, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 1 immediate container for each 5,000 immediate containers in such batch, but in no case less than 8 immediate containers.

(ii) For sterility testing; 10 immediate containers.

Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(3) If such batch is packaged for repacking or for use as an ingredient in the manufacture of another drug, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 5 packages, each containing approximately 0.5 gram.

(ii) For sterility testing; 10 packages, each containing approximately 40 milligrams.

Each such package shall be packaged in accordance with the requirements of paragraph (b) of this section.

(4) In connection with contemplated requests for certification of repacked batches of chloramphenicol or batches of another drug in the manufacture of which it is to be used, the manufacturer of a batch which is to be so repacked or used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (3) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $10.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i), (3) (i), and (4) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (2) (ii) and (3) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.302 Chloramphenicol capsules.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol capsules are capsules composed of chloramphenicol, with or without the addition of one or more suitable and harmless diluents, lubricants, colorings, and flavorings. The potency of each capsule is not less than 50 milligrams. The chloramphenicol used conforms to the requirements of § 146d.301 (a), except § 146d.301 (a) (2), (4), (5), and (6). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each chloramphenicol capsule is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *If it is intended for use by man.* In addition to the labeling prescribed by § 1.106(b) of this chapter, issued pursuant to section 502(f) of the act, each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement, "Warning—Blood dyscrasias may be associated with the use of chloramphenicol. It is essential that adequate blood studies be made. (See enclosed warnings and precautions.)"

(*b*) The statement "Expiration date ----------," the blank being filled in with the date that is 60 months after the month during which the batch was certified.

(ii) The circular or other labeling within or attached to the package, bearing directions, precautions, and warnings for its use by physicians, shall begin with the following statements, which shall be underscored or italicized:

(*a*) "Warning—Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms that are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective; or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat; or as a prophylactic agent."

(*b*) "Precautions—It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia."

(2) *If it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements of subparagraph (1) of this paragraph except subdivisions (i)(*a*) and (ii), and in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions, precautions, and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chloramphenicol capsules shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chloramphenicol used in making such batch was completed, the number of milligrams in each capsule, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and

assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per capsule.

(ii) The chloramphenicol used in making the batch; potency, toxicity, specific rotation, melting point, and absorptivity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one capsule for each 5,000 capsules in the batch, but in no case less than 30 capsules, collected by taking single capsules at such intervals throughout the entire time of preparation that the quantities encapsulated during the intervals are approximately equal.

(ii) The chloramphenicol used in making the batch; ten packages, each containing approximately equal portions of not less than 300 milligrams each, packaged in accordance with the requirements of § 146d.301 (b).

(iii) In case of an initial request for certification, each diluent, lubricant, coloring, and flavoring used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of chloramphenicol capsules under the regulations in this part shall be:

(1) $0.75 for each capsule in the sample submitted in accordance with paragraph (d) (3) (i) of this section, $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such capsules and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.303 Chloramphenicol ointment (chloramphenicol cream).

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol ointment is chloramphenicol in a suitable and harmless ointment base, with or without suitable and harmless buffer substances, dispersing and suspending agents. It may contain cortisone or a suitable derivative of cortisone. If such base is water-miscible, it shall contain a suitable and harmless preservative. Its potency is not less than 1.0 milligram per gram. The chloramphenicol used conforms to the requirements of § 146d.301 (a), except subparagraphs (2), (3), (4), and (5), of that paragraph. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless it is packaged in a single dose container, chloramphenicol ointment shall be packaged in collapsible tubes, which shall be well-closed containers as defined by the U. S. P., and shall not be larger than the ⅛-ounce size if such ointment is represented for ophthalmic use, and in no case larger than the 2-ounce size, except that if it is labeled solely for hospital use it may be packaged in immediate containers of glass which meet the test for tight containers as defined by the U. S. P. The composition of the immediate container and closure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container the statement "Expiration date ----------," the blank being filled in with the date that is 60 months, or 24 months if it is packaged in an immediate container other than tin or glass, or 12 months if the ointment base is water miscible, after the month during which the batch was certified.

(ii) If it contains one of the active ingredients specified in paragraph (a) of this section, after the name "chloramphenicol ointment," wherever it appears, the name of the active ingredient, in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chloramphenicol ointment shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chloramphenicol used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that each component of the ointment base used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per gram.

(ii) The chloramphenicol used in making the batch; potency, pH, specific rotation, melting point, and absorptivity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; 1 package for each 5,000 packages in the batch, but in no case less than 5 packages if it is packaged in immediate containers of tin or glass, and not less than 20 immediate containers if it is packaged in immediate containers other than tin or glass, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chloramphenicol used in making the batch; 10 packages, each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146d.301 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 200 grams, except if cortisone or a derivative of cortisone is used, such package shall contain approximately 100 milligrams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each multiple-dose package or $1.00 for each single-dose container in the sample submitted in accordance with paragraph (d) (3) (i) of this section, and $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; and

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.304 Chloramphenicol ophthalmic.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol ophthalmic is chloramphenicol, with or without one or more suitable and harmless preservatives, buffer substances, and diluents. It may contain cortisone hydrocortisone, or a suitable ester of cortisone or hydrocortisone. It is sterile. The chloramphenicol is of such quantity that when prepared as directed in its labeling the potency of such solution or suspension is not less than 1.0 milligram per milliliter and maintains its labeled potency after it has been kept for 10 days at room temperature. Such solution or suspension has a pH of 7.3±0.2. The chloramphenicol used conforms to the requirements of § 146d.301 (a), except subparagraphs (2), (4), and (5) of that paragraph. Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container of chloramphenicol ophthalmic shall be a tight container as defined by the U. S. P. Its closure shall be one through which a hypodermic needle cannot be introduced. The composition of the immediate container and closure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container may be packaged in combination with a container of the solvent, sterile distilled water U. S. P.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement "Expiration date ----------," the blank being filled in with the date that is 60 months after the month during which the batch was certified.

(*b*) If it is packaged in combination with a container of a solvent, the statement "*Warning*—Not for injection."

(ii) If it contains one of the active ingredients specified in paragraph (a) of this section, after the name "chloramphenicol ophthalmic," wherever it appears, the name of such ingredient, in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chloramphenicol ophthalmic shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless previously submitted) the date on which the latest assay of the chloramphenicol used in making such batch was completed, the number of milligrams of chloramphenicol in each immediate container, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each other ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section. If such batch or any part thereof is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, and pH of the solution or suspension prepared as directed in its labeling.

(ii) The chloramphenicol used in making the batch; potency, toxicity, pH, specific rotation, melting point, and absorptivity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chloramphenicol used in making the batch; 10 packages, each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146d.301 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing aproximately 5.0 grams, except if cortisone acetate is used, such package shall contain approximately 100 milligrams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container or package in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.305 Chloramphenicol palmitate.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol palmitate is the white to grayish-white, tasteless, crystalline palmitic acid ester of chloramphenicol. It is so purified and dried that:

(1) It contains not less than 555 micrograms and not more than 595 micrograms of chloramphenicol per milligram.

(2) It is nontoxic.

(3) Its melting point is 89°±3° C.

The chloramphenicol used conforms to the requirements of § 146d.301 (a), except subparagraphs (2), (4), and (5) of that paragraph.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of chloramphenicol palmitate shall bear on its outside wrapper or container and the immediate container, as hereinafter indicated, the following:

(1) The batch mark.

(2) The number of grams in the immediate container and the number of milligrams of chloramphenicol per gram.

(3) The statement "Expiration date ----------," the blank being filled in with the date which is 48 months after the month during which the batch was certified.

(4) The statement "For manufacturing use only."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of chloramphenicol palmitate shall submit with his request a statement showing the batch mark, the number of packages of

each size in the batch and (unless it was previously submitted) the date on which the latest assay of the drug comprising such batch was completed. Such request shall be accompanied or followed by results of tests and assays made by him on the batch for potency, toxicity and melting point.

(2) Such person shall submit with his request a sample containing 10 approximately equal portions of at least 300 milligrams, each taken from different parts of such batch; each such portion shall be packaged in a separate container and in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.306 Chloramphenicol palmitate oral suspension.

(a) *Standards of identity, strength, quality and purity.* Chloramphenicol palmitate oral suspension is chloramphenicol palmitate and one or more suitable and harmless buffer substances, suspending agents, preservatives, colorings, and flavorings, with or without one or more suitable and harmless vitamin substances, suspended in a suitable and harmless vehicle. It contains not less than 25 milligrams of chloramphenicol per milliliter. Its pH is not less than 4.5 and not more than 7.0. The chloramphenicol palmitate used conforms to the requirements of § 146d.305 (a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *If it is intended for use by man.* In addition to the labeling prescribed by § 1.106(b) of this chapter, issued pursuant to section 502(f) of the act, each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement, "Warning—Blood dyscrasias may be associated with the use of chloramphenicol. It is essential that adequate blood studies be made. (See enclosed warnings and precautions.)"

(*b*) The statement "Expiration date _____," the blank being filled in with the date that is 48 months after the month during which the batch was certified or with the date that is 24 months after the month during which the batch was certified if it contains one or more vitamin substances.

(ii) The circular or other labeling within or attached to the package, bearing directions, precautions, and warnings for its use by physicians, shall begin with the following statements, which shall be underscored or italicized:

(*a*) "Warning—Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms that are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective; or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat; or as a prophylactic agent."

(*b*) "Precautions—It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia."

(2) *If it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements of subparagraph (1) of this paragraph, except subdivisions (i) (*a*) and (ii), and in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions, precautions, and warnings adequate for the veterinary use of the drug by the laity.

(3) On the label and labeling, if it contains one or more vitamin substances, after the name "chloramphenicol palmitate oral suspension," wherever it appears, the words "with vitamin _____," the blank being filled in with the name of the vitamin ingredient used, or "with vitamins," if it contains more than one vitamin ingredient, in juxtaposition with such name.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark, and (unless it was previously submitted) the date on which the latest assay of the chloramphenicol palmitate used in making such batch was completed, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per milliliter, pH.

(ii) The chloramphenicol palmitate used in making the batch; potency, toxicity, melting point, absorptivity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one package for each 5,000 packages in the batch, but in no case less than 5, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chloramphenicol palmitate used in making the batch; 10 packages, each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146d.305 (b).

(iii) In the case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.307 Chloramphenicol solution; chloramphenicol for aqueous injection.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol solution is chloramphenicol, with or without one or more suitable and harmless buffer substances, dissolved in one or more suitable and harmless solvents. Chloramphenicol for aqueous injection

is a dry mixture of chloramphenicol and one or more suitable and harmless suspending or dispersing agents, buffer substances, and preservatives. It is so purified that:

(1) If it is the solution of the drug, its potency is 250 milligrams per milliliter.

(2) It is sterile.

(3) It is nontoxic.

(4) It is nonpyrogenic.

(5) It contains no histamine nor histamine-like substances.

(6) If it is chloramphenicol solution, its pH is not less than 4.7 and not more than 5.0. If it is the dry mixture of the drug, the pH of a suspension prepared as directed in its labeling is not less than 4.5 and not more than 7.5.

The chloramphenicol used conforms to the requirements of § 146d.301 (a). Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing and it is the solution of the drug, it shall be in hermetically sealed, colorless, transparent glass ampuls, each of which shall contain 2.0 milliliters. If it is packaged for dispensing and it is the dry mixture of the drug, it shall be in colorless, transparent glass containers, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness, and each such container shall contain 1.0 gram or 2.0 grams of chloramphenicol.

(c) *Labeling*—(1) *If it is intended for use by man.* In addition to the labeling prescribed by § 1.106(b) of this chapter, issued pursuant to section 502(f) of the act, each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement, "Warning—Blood dyscrasias may be associated with the use of chloramphenicol. It is essential that adequate blood studies be made. (See enclosed warnings and precautions.)"

(*b*) The statement "Expiration date ----------," the blank being filled in with the date that is 24 months after the month during which the batch was certified if it is the solution of the drug, or 48 months after the month during which the batch was certified if it is the dry mixture of the drug: *Provided, however,* That such expiration date may be omitted from the immediate container if it contains a single dose and it is packaged in an individual wrapper or container.

(*c*) If it is the dry mixture of the drug, the statement "For intramuscular use only."

(ii) On the outside wrapper or container, if it is the solution of the drug, the statement "Store in refrigerator not above 15° C. (59° F.)."

(iii) The circular or other labeling within or attached to the package, bearing directions, precautions, and warnings for its use by physicians, shall begin with the following statements, which shall be underscored or italicized:

(*a*) "Warning—Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms that are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective; or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat; or as a prophylactic agent."

(*b*) "Precautions—It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia."

(2) *If it is intended solely for veterinary use.* Its label and labeling shall comply with all the requirements of subparagraph (1) of this paragraph except subdivisions (i) (*a*) and (iii), and in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions, precautions, and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages in the batch, the number of milligrams or grams in each of such packages, the date on which the latest assay of the drug comprising the batch was completed, the batch mark and (unless it was previously submitted) the date on which the latest assay of the chloramphenicol used in making such batch was completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, toxicity, pyrogens, histamine content, and pH.

(ii) The chloramphenicol used in making the batch; potency, specific rotation, melting point, and absorptivity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in such batch, but in no case less than 8 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chloramphenicol used in making the batch; two immediate containers containing approximately 300 milligrams each, packaged in accordance with the requirements of § 146d.301 (b).

(iii) In case of an initial request for certification, each ingredient (unless it is recognized by the U. S. P. or N. F.) used in making the batch; one package of each, containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $10.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.308 Chloramphenicol otic; chloramphenicol topical.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol otic and chloramphenicol topical is chloramphenicol, with or without ethyl aminobenzoate, in a suitable and harmless vehicle. The potency of the solution is not less than 5 milligrams per milliliter. Its moisture content is not more

than 2 percent. Its pH is not less than 4 and not more than 8. The chloramphenicol used conforms to the requirements of § 146d.301(a), except subparagraphs (2), (3), (4), and (5) of that paragraph. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Each immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the following:

(i) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(ii) The statement "*Warning*—For external use only."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(2) On the outside wrapper or container, if it is packaged for dispensing and it is intended for use by man, a reference specifically identifying a readily available medical publication containing information (including contraindications and possible sensitization) adequate for the use of such drug by practitioners licensed by law to administer it; or a reference to a brochure or other printed matter containing such information, and a statement that such brochure or other printed matter will be sent on request: *Provided, however,* That this reference may be omitted if the information is contained in a circular or other labeling within or attached to the package.

(3) On the circular or other labeling within or attached to the package, if it is packaged for dispensing and it is intended solely for veterinary use and is conspicuously so labeled, adequate directions and warnings for the veterinary use of such drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch the batch mark, and (unless it was previously submitted) the date on which the latest assay of the chloramphenicol used in making the batch was completed, the number of milligrams of chloramphenicol in each milliliter of the batch, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each other ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, moisture, and pH.

(ii) The chloramphenicol used in making the batch; potency, pH, specific rotation, melting point, and absorptivity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 20 immediate containers, collected by taking single immediate containers, before or after labeling, at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The chloramphenicol used in making the batch; 10 packages, each containing approximately equal portions of not less than 300 milligrams, packaged in accordance with the requirements of § 146d.301 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 5.0 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $1.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification, unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146d.309 Chloramphenicol-streptomycin capsules; chloramphenicol-dihydrostreptomycin capsules.

(a) Chloramphenicol - streptomycin capsules and chloramphenicol-dihydrostreptomycin capsules conform to all requirements prescribed by § 146d.302 for chloramphenicol capsules, and are subject to all procedures prescribed by § 146d.302 for chloramphenicol capsules, except that:

(1) Each capsule contains not less than 125 milligrams of chloramphenicol.

(2) Each capsule contains not less than 125 milligrams of streptomycin or dihydrostreptomycin. The streptomycin used conforms to the standards prescribed therefor by § 146b.101 (a) of this chapter, except § 146b.101 (a) (2), (4), and (5). The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103 of this chapter, except the standards for sterility, pyrogens, and histamine content.

(3) Its moisture content is not more than 5 percent.

(4) Its expiration date shall be 48 months after the month during which the batch was certified.

(5) In addition to complying with the requirements of § 146d.302 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, toxicity, moisture, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin sulfate. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages each containing approximately equal portions of not less than 500 milligrams of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101(b) of this chapter.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (5) of this section shall be:

(1) $1.00 for each capsule submitted.

(2) $4.00 for each immediate container of the streptomycin or dihydrostreptomycin submitted.

§ 146d.310 Chloramphenicol tablets.

Chloramphenicol tablets are tablets that conform to all requirements and are subject to all procedures prescribed by § 146d.302 for chloramphenicol capsules, except that the expiration date of such tablets shall be 24 months after the month during which the batch was certified. In addition to the requirements prescribed by § 146d.302, tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. A person who requests certification shall submit for disintegration-time studies

results of this test made by him and a sample of 6 tablets. The fee for the tablets submitted for the disintegration-time studies shall be $3.00.

§ 146d.311 Chloramphenicol palmitate-streptomycin oral suspension; chloramphenicol palmitate-dihydrostreptomycin oral suspension.

Chloramphenicol palmitate-streptomycin oral suspension and chloramphenicol palmitate-dihydrostreptomycin oral suspension conform to all requirements and are subject to all procedures prescribed by § 146d.306 for chloramphenicol palmitate oral suspension, except that:

(a) It contains not less than 30 milligrams of streptomycin or dihydrostreptomycin per milliliter. The streptomycin used conforms to the standards prescribed by § 146b.101 (a) of this chapter, except § 146b.101 (a) (2), (4), (5), and (6). The dihydrostreptomycin used conforms to the standards prescribed therefor by § 146b.103 of this chapter, except the standards for sterility, pyrogens, moisture, and histamine content.

(b) Its expiration date shall be 48 months after the month during which the batch was certified.

(c) In addition to complying with the requirements of § 146d.306 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and date of the latest tests and assays of the streptomycin or dihydrostreptomycin used in making the batch for potency, toxicity, pH, streptomycin content if it is dihydrostreptomycin, and crystallinity if it is crystalline dihydrostreptomycin. He shall also submit in connection with his request a sample consisting of not less than 6 packages of the batch and (unless it was previously submitted) a sample consisting of not less than 5 packages containing approximately equal portions of not less than 0.5 gram each of the streptomycin or dihydrostreptomycin used in making the batch, packaged in accordance with the requirements of § 146b.101(b) of this chapter.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(1) $5.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of streptomycin or dihydrostreptomycin.

§ 146d.312 Chloramphenicol-neomycin ointment.

Chloramphenicol-neomycin ointment conforms to all requirements and is subject to all procedures prescribed by § 146d.303 for chloramphenicol in an oily base ointment, except that:

(a) It contains not less than 3.50 milligrams of neomycin per gram. The neomycin used conforms to the requirements prescribed for neomycin by § 146e.410 (a) (2) of this chapter, except the standard for toxicity.

(b) Its moisture content is not more than 1 percent.

(c) In lieu of the labeling prescribed by § 146d.303(c)(1)(i), each package shall bear on the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified.

(d) In addition to complying with the requirements of § 146d.303 (d), a person requesting certification of a batch shall submit with his request a statement showing the number of milligrams of chloramphenicol and the number of milligrams of neomycin in each gram of ointment, the batch mark, and (unless previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, moisture and pH. He shall also submit in connection with his request a sample consisting of not less than 6 packages of the ointment and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making the batch.

(e) The fee for the services rendered with respect to each immediate container in the sample of neomycin submitted in accordance with the requirements prescribed therefor by this section shall be $4.00.

§ 146d.313 Chloramphenicol-polymyxin ointment.

Chloramphenicol-polymyxin ointment conforms to all requirements and is subject to all procedures prescribed by § 146d.303 for chloramphenicol ointment, except that:

(a) It contains not less than 5,000 units of polymyxin B per gram. The polymyxin B used conforms to the requirements prescribed for polymyxin B by § 146b.107 (a) of this chapter.

(b) In lieu of the labeling prescribed by § 146d.303(c)(1)(i), each package shall contain on the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by this section; *Provided, however,* That such expiration date may be omitted from the immediate container if it contains a single dose and it is packaged in an individual wrapper or container.

(c) In addition to complying with the requirements of § 146d.303 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless previously submitted) the results and date of the latest tests and assays of the polymyxin used in making the batch for potency and toxicity. He shall also submit in connection with his request a sample consisting of not less than 6 packages of ointment and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the polymyxin used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) (3) of this section shall be:

(1) $5.00 for each tube of ointment.

(2) $4.00 for each immediate container of the polymyxin used in making the batch.

§ 146d.314 Chloramphenicol sodium succinate.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol sodium succinate is the light-yellow, water-soluble, ethanol-insoluble crystalline sodium salt of the 3-monosuccinate ester of chloramphenicol. It is so purified and dried that:

(1) Its potency is not less than 650 μg. per milligram.

(2) It is sterile.

(3) It is nontoxic.

(4) It is nonpyrogenic.

(5) It contains no histamine nor histamine-like substances.

(6) Its moisture content is not more than 5.0 percent.

(7) The pH of an aqueous solution containing 200 milligrams per milliliter is not less than 6.4 and not more than 7.0.

(8) Its specific rotation in an aqueous solution containing 50 milligrams per milliliter at 25° C. is $+6.5° \pm 1.5°$.

(b) *Packaging; labeling; request for certification, samples; fees.* Chloramphenicol sodium succinate conforms to all requirements and procedures prescribed for chloramphenicol by § 146d.301 (b), (c), (d), and (e), except that:

(1) The expiration date shall be the date that is 36 months after the month during which the batch was certified.

(2) The request for certification shall be accompanied or followed by the results of tests and assays of the batch for potency, sterility, toxicity, pyrogens, histamine, moisture, pH, and specific rotation.

(3) When a batch is packaged for repacking or for use as an ingredient in the manufacture of another drug, each package submitted for sterility testing shall contain approximately 500 milligrams of the drug in lieu of 40 milligrams.

§ 146d.315 Chloramphenicol sodium succinate for aqueous injection.

(a) *Standards of identity, strength, quality, and purity.* Chloramphenicol sodium succinate for aqueous injection is a dry mixture of chloramphenicol sodium succinate and one or more suitable and harmless buffer substances and preservatives. It is so purified that:

(1) It is sterile.

(2) It is nontoxic.

(3) It is nonpyrogenic.

(4) It contains no histamine nor histamine-like substances.

(5) Its moisture content is not more than 5 percent.

(6) The pH of a solution prepared as directed in its labeling is not less than 6.4 and not more than 7.0.

The chloramphenicol sodium succinate used conforms to the requirements prescribed by § 146d.314(a), except that it is exempt from the requirements of § 146d.314(a) (2) and (4) when the chloramphenicol sodium succinate for aqueous injection, in which it is used, has been rendered sterile and pyrogen-free. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees.* Chloramphenicol sodium succinate for aqueous injection conforms to the requirements and procedures prescribed by § 146d.307 (b), (c), (d), and (e) for chloramphenicol for aqueous injection, except that:

(1) The expiration date of the drug shall be 36 months.

(2) In lieu of the requirements specified by § 146d.307(d)(2), a person who requests certification of a batch shall submit in connection with his request results of tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Potency, sterility, toxicity, pyrogens, histamine content, moisture, and pH.

(ii) The chloramphenicol sodium succinate used in making the batch: Potency and specific rotation.

§ 146d.316 Chloramphenicol-paromomycin ointment.

Chloramphenicol-paromomycin ointment conforms to all requirements and procedures prescribed by § 146d.303 for chloramphenicol ointment, except that:

(a) Each gram contains not less than 5 milligrams of paromomycin activity, as the sulfate. The paromomycin used is the sulfate salt of a kind of paromomycin produced by the growth of Streptomyces rimosus var. paromomycinus. It is a creamy-white to light-yellow powder. Its potency is not less than 635 micrograms per milligram on an anhydrous basis. Its pH in a 3 percent aqueous solution is not less than 5.0 and not more than 7.5. Its moisture content is not more than 5.0 percent. Its specific rotation in water is +50° to +55° on an anhydrous basis. Its ash content is not more than 2.0 percent.

(b) In addition to the labeling prescribed for chloramphenicol ointment by § 146d.303, each package shall bear on its label and labeling the number of milligrams of paromomycin activity in each gram of the batch. The expiration date of the drug shall be 24 months. Each package shall bear on a circular or other labeling within or attached to the package adequate directions and warnings for use of the drug by practitioners licensed by law to administer it.

(c) In addition to complying with § 146d.303(d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and the date of the latest tests and assays of the paromomycin sulfate used in making the batch for potency, pH, moisture, specific rotation, and ash content. He shall also submit in connection with his request a sample consisting of not less than 6 immediate containers of the batch and (unless it was previously submitted) a sample consisting of 10 packages, each containing approximately equal portions of not less than 500 milligrams of the paromomycin sulfate used in making the batch.

(d) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (c) of this section shall be:

(1) $5.00 for each immediate container in the sample of the batch.

(2) $5.00 for each immediate container in the sample of paromomycin sulfate used in making the batch.

PART 146e—CERTIFICATION OF BACITRACIN AND BACITRACIN-CONTAINING DRUGS

Sec.

146e.401 Bacitracin.
146e.402 Bacitracin ointment; zinc bacitracin ointment.
146e.403 Bacitracin tablets; zinc bacitracin tablets; bacitracin methylene disalicylate tablets; bacitracin suppositories; zinc bacitracin suppositories (if they are represented for vaginal use); bacitracin implantation pellets; zinc bacitracin implantation pellets (if they are represented for use by implanting under the skin of animals).
146e.404 Bacitracin troches; zinc bacitracin troches.
146e.405 Bacitracin with vasoconstrictor; bacitracin with ____ (the blank being filled in with the common or usual name of the vasoconstrictor).
146e.406 Bacitracin-tyrothricin troches; zinc bacitracin-tyrothricin troches.
146e.407 Bacitracin-tyrothricin ointment.
146e.408 Bacitracin ophthalmic.
146e.409 Bacitracin-polymyxin ointment; zinc bacitracin-polymyxin ointment.
146e.410 Bacitracin-neomycin tablets; zinc bacitracin-neomycin tablets; bacitracin methylene disalicylate-neomycin tablets.
146e.411 Bacitracin-neomycin ointment; zinc bacitracin-neomycin ointment.
146e.412 Bacitracin-polymyxin tablets.
146e.413 Bacitracin-neomycin troches; zinc bacitracin-neomycin troches.
146e.414 Bacitracin-neomycin with vasoconstrictor; bacitracin-neomycin with ____ (the blank being filled in with the common or usual name of the vasoconstrictor).
146e.415 Bacitracin-polymyxin troches; zinc bacitracin-polymyxin troches.
146e.416 Bacitracin methylene disalicylate.
146e.417 Powder bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.
146e.418 Zinc bacitracin (bacitracin zinc salt).
146e.419 Bacitracin - neomycin - polymyxin troches; zinc bacitracin-neomycin-polymyxin troches.
146e.420 Bacitracin - tyrothricin - neomycin troches; bacitracin-gramicidin-neomycin troches; zinc bacitracin-tyrothricin-neomycin troches; zinc bacitracin-gramicidin-neomycin troches.
146e.421 Bacitracin - neomycin - polymyxin tablets.
146e.422 Bacitracin - polymyxin - neomycin ointment.
146e.423 Soluble bacitracin methylene disalicylate.
146e.424 Bacitracin - neomycin - polymyxin with vasoconstrictor; bacitracin-neomycin-polymyxin with ____ (the blank being filled in with the common or usual name of the vasoconstrictor).
146e.425 Bacitracin powder.
146e.426 Tablets bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.
146e.427 Feed grade bacitracin powder oral veterinary (crude bacitracin powder oral veterinary, unrefined bacitracin powder oral veterinary); feed grade zinc bacitracin powder oral veterinary (crude zinc bacitracin powder oral veterinary, unrefined zinc bacitracin powder oral veterinary).
146e.428 Capsules bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.
146e.429 Bacitracin-neomycin in oil veterinary.
146e.430 Bacitracin - neomycin - polymyxin powder topical; zinc bacitracin-neomycin-polymyxin powder topical.
146e.431 Feed grade manganese bacitracin powder oral veterinary.

AUTHORITY: §§ 146e.401 to 146e.431 issued under 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 146e.401 Bacitracin.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin is a white to brown, neutral water-soluble polypeptide. It is so purified and dried that:

(1) Its potency is not less than 40 units per milligram, except that if it is packaged for dispensing and it is intended for systemic medication its potency is not less than 50 units per milligram;

(2) It is sterile.

(3) It is nontoxic.

(4) It is nonpyrogenic.

(5) Its moisture content is not more than 5 percent.

(6) Its pH in aqueous solution of 10,000 units per milliliter is not less than 5.5 and not more than 7.5.

(7) Its ash content is not more than 3.0 percent.

(8) If it is intended for systemic medication, its heavy metals content is not more than 30 parts per million.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying the seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

In case it is packaged for dispensing, it shall be in immediate containers of colorless transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness; each such container shall contain not more than 60,000 units (unless it is intended solely for veterinary use and is conspicuously so labeled) and may be packaged in combination with a container of the solvent, water for injection U. S. P., physiological salt solution U. S. P., or with a container of an aqueous solution of a suitable local anesthetic.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified, except if it is packaged for dispensing and it is intended for systemic medication the blank shall be filled in with the date that is 24 months after the month during which the batch was certified, and except that the blank may be filled in with the date that is 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug complies with the standards prescribed by paragraph (a) of this section.

(ii) On the outside wrapper or container, if it is packaged for dispensing and it is intended for systemic medication the statement "Store in refrigerator not above 15° C. (59° F.)" or "Store below 15° C. (59° F.)."

(iii) On the circular or other labeling within or attached to the package, the conditions under which such solutions should be stored, including a reference to their instability when stored under other conditions; and the statement "Sterile solution may be kept in refrigerator for 1 week without significant loss of potency."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with the requirements prescribed by subparagraph (1) (i), (ii), and (iii) of this paragraph and with the requirements prescribed by § 1.106(c) of this chapter.

(3) *It is packaged solely for manufacturing use and/or repacking.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The number of units of bacitracin per milligram or per gram and the number of grams or kilograms in the immediate container.

(ii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iii) The statement "For manufacturing use," "For repacking," or "For manufacturing use or repacking."

(iv) The information required by subparagraph (1) (i) and (ii) of this paragraph.

(d) *Request for certification, check tests and assays; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of bacitracin shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of units in each package, and (unless it was previously submitted) the date on which the latest assay of the drug comprising the batch was completed. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, sterility, toxicity, pyrogens, moisture, pH, ash content, and heavy metals. If such batch or any part thereof is to be packaged with a solvent such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) If such batch is packaged for dispensing, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility, one immediate container for each 5,000 immediate containers in such batch, but in no case less than six immediate containers. If a sample of such batch has not been previously submitted in accordance with subparagraph (3) or (4) of this paragraph, such person shall also submit one additional package containing 1.0 gram of the batch.

(ii) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(3) If such batch is packaged for repacking or for use as an ingredient in the manufacture of another drug, such person shall submit with his request an accurately representative sample of the batch, consisting of the following:

(i) For all tests except sterility; 6 packages.

(ii) For sterility testing; 10 packages.

Each such package shall contain approximately 0.5 gram, taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(4) In connection with contemplated requests for certification of repacked batches or batches of another drug in the manufacture of which it is to be used, the manufacturer of a batch which is to be so repacked or used may request the Commissioner to make check tests and assays on a sample of such batch, taken as prescribed by subparagraph (3) of this paragraph. From the information required by subparagraph (1) of this paragraph may be omitted results of tests and assays not required for the batch when used in such other drug. The Commissioner shall report to such manufacturer results of such check tests and assays as are so requested.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (2) (i), (3) (i), and (4) of this section; $10.00 for all containers submitted in accordance with paragraphs (d) (2) (ii) and (d) (3) (ii) of this section.

(2) If the Commissioner considers that investigations, other than examination of such immediate containers, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.402 Bacitracin ointment; zinc bacitracin ointment.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin ointment and zinc bacitracin ointment are composed of bacitracin or zinc bacitracin in a suitable and harmless ointment base, or they are a powder composed of bacitracin or zinc bacitracin and one or more suitable and harmless diluents, dispersing agents, and preservatives which upon the addition of the quantity of water recommended in its labeling, produces an ointment. It may contain a suitable local anesthetic, cortisone, or a suitable derivative of cortisone, one or more suitable sulfonamides, one or more suitable proteolytic enzymes, and, if it is intended solely for veterinary use and is conspicuously so labeled, one or more suitable antifungal agents or rotenone. Its potency is not less than 500 units per gram. Its moisture content is not more than 1 percent, except if it is a powder its moisture content is not more than 5 percent. The zinc bacitracin used conforms to the standards prescribed therefor by § 146e.418 (a), except § 146e.418 (a) (2). The bacitracin used conforms to the standards prescribed therefor by § 146e.401 (a), except § 146e.401 (a) (2), (3), (4), and (8). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* If it is bacitracin or zinc bacitracin in an ointment base it shall be packaged in collapsible tubes, which shall be well-closed containers as defined by the U. S. P., and which shall not be larger than the 2-ounce size, except if it is labeled solely for hospital use; but in no case shall such ointment be packaged in containers other than collapsible tubes if it is labeled for ophthalmic use, and such tubes shall not be

larger than the ⅛-ounce size. If it is a powder, it shall be packaged in immediate containers of glass which meet the tests for tight containers as defined by the U. S. P. The composition of the immediate container and closure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for ophthalmic use by man or it is intended for use by man and it contains a sulfonamide, or cortisone, or a derivative of cortisone, or a proteolytic enzyme.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement "Expiration date ----------," the blank being filled in with the date that is not more than 36 months after the month during which the batch was certified, except if it is zinc bacitracin ointment or if it contains one or more proteolytic enzymes, the blank is filled in with the date that is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 48 months or 60 months, after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(*b*) If it is a powder, the statement "After the addition of water, the ointment may be stored in the refrigerator for 1 week without significant loss of potency."

(ii) If it contains in addition to bacitracin or zinc bacitracin, one or more other active ingredients specified in paragraph (a) of this section, after the name "bacitracin ointment," wherever such name appears, the words "with ----------," in juxtaposition with such name, the blank being filled in with the common or usual name of each such other ingredient.

(2) *It is intended for use by man, it is not packaged for ophthalmic use and it does not contain a sulfonamide, or cortisone, or a derivative of cortisone, or a proteolytic enzyme.* Its label and labeling shall comply with the requirements of subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," the labeling of each package shall bear information that the drug is for use only in the prevention of infections in minor cuts and abrasions and a statement that use of the drug should be discontinued and a physician consulted if signs of infection or irritation appear.

(3) *It is packaged for dispensing, it contains 9α-fluorohydrocortisone (fludrocortisone) and it is intended solely for veterinary use.* Its label and labeling shall comply with the requirements of §1.106(c) of this chapter (regulations issued under section 502(f) of the act) and with the requirements of subparagraph (1) of this paragraph.

(4) *It is packaged for dispensing, it does not contain 9α-fluorohydrocortisone (fludrocortisone) and it is intended solely for veterinary use.* Its label and labeling shall comply with the requirements of subparagraph (3) of this paragraph, except that in lieu of the statement "Caution: Federal law restricts this drug to sale by or on the order of a licensed veterinarian" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall sumbit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the bacitracin or zinc bacitracin used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and that each component of the ointment base used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency and moisture.

(ii) The bacitracin or zinc bacitracin used in making the batch: potency, moisture, pH, ash content if it is bacitracin, and zinc content if it is zinc bacitracin.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one package for each 5,000 packages in the batch, but in no case less than 5 packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The bacitracin used in making the batch; six packages, each containing approximately equal portions of not less than 500 milligrams, packaged in accordance with the requirements of § 146e.401 (b).

(iii) The zinc bacitracin used in making the batch; 5 packages, each containing approximately equal portions of not less than 1.0 gram, packaged in accordance with the requirements of § 146e.418 (b).

(iv) In case of an initial request for certification, each other ingredient used in making the batch; one package of each containing approximately 200 grams, except if cortisone or a derivative of cortisone is used, such package shall contain approximately 100 milligrams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) or (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (i), (ii), (iii), and (iv) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

(f) *Exemption of bacitracin ointment and zinc bacitracin ointment from certification.* Bacitracin ointment and zinc bacitracin ointment shall be exempt from the requirements of sections 502(l) and 507 of the act if it complies with all the following conditions:

(1) It conforms to the standards of identity, strength, quality, and purity prescribed by paragraph (a) of this section.

(2) It does not contain an antifungal agent, or rotenone, or cortisone, or a derivative of cortisone, or a proteolytic enzyme.

(3) It is not the powder preparation decribed in paragraph (a) of this section.

(4) It conforms to the packaging and labeling requirements prescribed by this section.

(5) The labels bear an expiration date that is 36 months, if it is bacitracin ointment, or 24 months, if it is zinc bacitracin ointment, after the month during which the batch was last assayed and released by the manufacturer, except that the date that is 48 months or 60 months may be used if the manufacturer has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by paragraph (a) of this section.

§ 146e.403 Bacitracin tablets; zinc bacitracin tablets; bacitracin methylene disalicylate tablets; bacitracin suppositories; zinc bacitracin suppositories (if they are represented for vaginal use); bacitracin implantation pellets; zinc bacitracin implantation pellets (if they are represented for use by implanting under the skin of animals).

(a) *Standards of identity, strength, quality, and purity.* Bacitracin tablets, zinc bacitracin tablets, and bacitracin methylene disalicylate tablets are tablets composed of bacitracin, zinc bacitracin, or bacitracin methylene disalicylate, with or without kaolin and pectin and with or without one or more suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings, and with or without a suitable amebicidal agent. The potency of each tablet is not less than 1,000 units nor more than 10,000 units. Its moisture content is not more than 5 percent. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour. The bacitracin used conforms to the standards prescribed therefor by § 146e.401(a), except § 146e.401(a) (2), (4), and (8). The zinc bacitracin used conforms to the requirements of § 146e.-418(a). The bacitracin methylene disalicylate used conforms to the requirements of § 146e.416(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each tablet is enclosed in a foil or plastic film and such enclosure is a tight container as defined by the U. S. P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The immediate container may also contain a desiccant separated from the tablets by a plug of cotton or other like material. The composition of the immediate container, or of the foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label and labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, 36 months, or 48 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(ii) If it contains an amebicidal agent, kaolin, or pectin, after the name "bacitracin tablets," "zinc bacitracin tablets," or "bacitracin methylene disalicylate tablets," wherever it appears, the words "with _____," in juxtaposition with such name, the blank being filled in with the common or usual name of each such ingredient used.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the bacitracin, zinc bacitracin, or bacitracin methylene disalicylate used in making such batch was completed, the number of units in each tablet, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor, if any, by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Average potency per tablet, average moisture, and if required by paragraph (a) of this section, disintegration time.

(ii) The bacitracin, zinc bacitracin, or bacitracin methylene disalicylate used in making the batch; potency, toxicity, moisture, pH, ash content if it is bacitracin, and zinc content if it is zinc bacitracin.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) For potency and moisture: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets, collected by taking single tablets throughout the entire time of tableting so that the quantities tableted during the intervals are approximately equal.

(*b*) For disintegration time: 6 tablets.

(ii) The bacitracin used in making the batch; six packages, each containing approximately equal portions of not less than 500 milligrams each, packaged in accordance with the requirements of § 146e.401 (b).

(iii) The zinc bacitracin used in making the batch; 6 packages, each containing approximately equal portions of not less than 1.0 gram, packaged in accordance with the requirements of § 146e.418 (b).

(iv) The bacitracin methylene disalicylate used in making the batch; 5 packages containing approximately equal portions of not less than 5 grams each, packaged in accordance with the requirements of § 146e.416 (b).

(v) In case of an initial request for certification, each other substance used in making the batch; 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii), (iii), or (iv) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $0.75 for each tablet in the sample submitted in accordance with paragraph (d) (3) (i) (*a*) of this section; $3.00 for all tablets submitted in accordance with paragraph (d) (3) (i) (*b*) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), and (v) of this section.

(2) If the Commissioner considers that investigations, other than examination of such tablets and packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.404 Bacitracin troches; zinc bacitracin troches.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin troches and zinc bacitracin troches are troches composed of bacitracin or zinc bacitracin, with or without ethyl aminobenzoate and with or without one or more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. The potency of each troche is not less than 500 units. Its moisture content is not more than 5 percent. The bacitracin used conforms to the standards prescribed therefor by § 146e.401(a), except § 146e.401(a) (2), (4), and (8). The zinc bacitracin used conforms to the requirements of § 146e.-418(a). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Unless each troche is enclosed in foil or plastic film and such enclosure is a tight container as defined by the U.S.P., except the provision that it shall be capable of tight reclosure, the immediate container shall be a tight container as so defined. The

immediate container may also contain a desiccant separated from the troches by a plug of cotton or other like material. The composition of the immediate container, or foil or film enclosure, shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of troches shall bear, on its label or labeling as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark;

(ii) The number of units of bacitracin or zinc bacitracin and if it contains ethyl aminobenzoate, the quantity of such ingredient in each troche of the batch; and

(iii) The statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the use of such troches. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other uses of such troches by practitioners licensed by law to administer such drug will be sent to such practitioner upon request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the bacitracin or zinc bacitracin used in making such batch was completed, the number of units in each troche, the quantity of each ingredient used in making the batch, the date on which the latest assay of the troches comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency per troche and average moisture.

(ii) The bacitracin or zinc bacitracin used in making the batch; potency, moisture, toxicity, pH, ash content if it is bacitracin, and zinc content if it is zinc bacitracin.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; one troche for each 5,000 troches in the batch, but in no case less than 30 troches, collected by taking single troches at such intervals throughout the entire time the troches are being made, that the quantities made during the intervals are approximately equal.

(ii) The bacitracin used in making the batch; six packages, each containing approximately equal portions of not less than 500 milligrams, packaged in accordance with the requirements of § 146e.401 (b).

(iii) The zinc bacitracin used in making the batch; six packages, each containing approximately equal portions of not less than 1.0 gram, packaged in accordance with the requirements of § 146e.418 (b).

(iv) In case of an initial request for certification, each other substance used in making the batch; one package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the service rendered with respect to each batch under the regulations in this part shall be:

(1) $0.75 for each troche in the sample submitted in accordance with paragraph (d) (3) (i) of this section, $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii) and (iii) of this section; and

(2) If the Commissioner considers that investigations, other than examination of such troches, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.405 Bacitracin with vasoconstrictor; bacitracin with _____ (the blank being filled in with the common or usual name of the vasoconstrictor).

(a) *Standards of identity, strength, quality, and purity.* Bacitracin with vasoconstrictor is a dry mixture of bacitracin and a suitable vasoconstrictor, with or without suitable and harmless buffer substances, preservatives, colorings, and flavorings, or it is a packaged combination of one immediate container of bacitracin and one immediate container of a solution of a suitable vasoconstrictor, with or without suitable and harmless buffer substances, preservatives, colorings, and flavorings. The bacitracin is of such quantity that when dissolved as directed the potency of such solution is not less than 200 units per milliliter, and maintains its labeled potency after it has been kept for 7 days at room temperature. Such solution is isotonic, and has a pH of 6.0, ±0.5. The moisture content of the dry mixture of bacitracin with vasoconstrictor is not more than 5 percent. The bacitracin used conforms to the requirements of § 146e.401 (a), except subparagraphs (2), (4), and (8) of that paragraph. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* Each immediate container shall be a tight container as defined by the U. S. P. and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. The immediate container of the dry mixture of bacitracin with vasoconstrictor may be packaged in combination with an immediate container of a suitable diluent.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label and labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container of the bacitracin when it is a packaged combination of one immediate container of bacitracin and one immediate container of a vasoconstrictor, the statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified; if it is the dry mixture of bacitracin with vasoconstrictor, the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 24 months, 36 months, or 48 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(ii) On the outside wrapper or container and on the immediate container of the solution in the combination:

(*a*) A statement giving the method of dissolving the bacitracin and, if it is not a packaged combination, a statement that distilled water should be used.

(*b*) The conditions under which the solution should be stored, including a reference to its instability when stored under other conditions, and a statement "The solution may be kept at room temperature for 1 week without significant loss of potency."

(*c*) The statement "*Warning*—Not for injection."

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its

label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of bacitracin with vasoconstrictor shall submit with his request a statement showing the batch mark, the number of packages in such batch, the number of units in each immediate container, and (unless it was previously submitted) the date on which the latest assay of the bacitracin included in such batch was completed, the quantity of each ingredient used in making the batch of the dry mixture of bacitracin with vasoconstrictor, the quantity of each ingredient used in making the solution included in the packaged combination, and a statement that such solution conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The bacitracin included in the packaged combination and the bacitracin used in making the batch of the dry mixture of bacitracin with vasoconstrictor; potency, toxicity, moisture, pH and ash content.

(ii) The solution after the bacitracin has been dissolved therein; potency.

(iii) The batch of the dry mixture of bacitracin with vasoconstrictor; potency and moisture.

(3) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch:

(*a*) If it contains only bacitracin and the bacitracin used has been previously submitted, or it contains bacitracin and other ingredients; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers.

(*b*) If it contains only bacitracin and the bacitracin used has not been previously submitted; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 12 immediate containers.

Such sample shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The bacitracin used in making the batch of the dry mixture of bacitracin with vasoconstrictor; six packages, each containing approximately equal portions of not less than 500 milligrams each, packaged in accordance with the requirements of § 146e.401 (b).

(iii) In case of an initial request for certification of a batch of a dry mixture of bacitracin with vasoconstrictor, each other substance used in making the batch; one package of each containing approximately 5 grams.

(iv) In case of an initial request for certification of the packaged combination of bacitracin with vasoconstrictor, or when any change is made in the composition of such solution; five packages of the solution included in the combination.

(4) No result referred to in subparagraph (2) (i) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, are required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch of bacitracin with vasoconstrictor under the regulations in this part shall be:

(1) $4.00 for each immediate container submitted in accordance with paragraph (d) (3) (i), (ii), (iii), and (iv) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.406 Bacitracin-tyrothricin troches; zinc bacitracin-tyrothricin troches.

(a) Bacitracin-tyrothricin troches and zinc bacitracin-tyrothricin troches conform to all requirements and are subject to all procedures prescribed by § 146e.404 for bacitracin troches and zinc bacitracin troches, except that:

(1) Each troche contains not less than 50 units of bacitracin or zinc bacitracin.

(2) Each troche contains not less than 1 milligram of tyrothricin.

(3) Each troche may be tableted with or without ethyl aminobenzoate.

(b) In lieu of the directions prescribed for bacitracin troches and zinc bacitracin troches by § 146e.404 (c) (1) (ii) each package shall bear on the outside wrapper or container and the immediate container the number of units of bacitracin or zinc bacitracin and the number of milligrams of tyrothricin and ethyl aminobenzoate in each troche of the batch.

(c) The fee for the services rendered with respect to each troche in the sample submitted in accordance with the requirements of this section shall be $1.00.

§ 146e.407[1] Bacitracin-tyrothricin ointment.

(a) Bacitracin-tyrothricin ointment conforms to all requirements prescribed by § 146e.402 for bacitracin ointment, and is subject to all procedures prescribed by § 146e.402 for bacitracin ointment, except paragraph (f) of that section, and except that:

(1) It contains not less than 0.5 milligram of tyrothricin per gram of ointment.

(2) [Reserved.]

(3) In lieu of the samples required by § 146e.402 (d) (3) (i), a minimum of 6 packages of the batch should be submitted.

(b) The fee for the services rendered with respect to each tube of ointment in the sample submitted under the regulations in this section shall be $5.00.

§ 146e.408 Bacitracin ophthalmic.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin ophthalmic is bacitracin, with or without one or more suitable and harmless preservatives, local anesthetics, buffer substances, and diluents. It is sterile. Its moisture content is not more than 5 percent. The bacitracin is of such quantity that when dissolved as directed in its labeling the potency of such solution is not less than 500 units per milliliter and maintains its labeled potency after it has been kept for 7 days at room temperature. Such solution has a pH of 6.5±0.5. The bacitracin used conforms to the requirements of § 146e.401(a), except § 146e.401 (a) (2), (4), and (8). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* The immediate container of bacitracin ophthalmic shall be a tight container as defined by the U. S. P.; its closure shall be one through which a hypodermic needle cannot be introduced; and the immediate container and closure shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container shall contain not less than 5,000 units, and each may be packaged in combination with a container of the solvent, sterile distilled water U. S. P.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified.

(*b*) The statement "*Warning*—Not for injection."

(ii) If a local anesthetic is present, after the name "bacitracin ophthalmic," wherever it appears, the words "with _____ (the blank being filled in with the common or usual name of the local anesthetic)," in juxtaposition with such name.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Requests for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the bacitracin used in making such batch was completed, the number of units in each immediate container, the date on which the latest assay of the drug comprising such batch was completed, the quantity of each other ingredient used in making the batch, and a statement that each such ingredient used conforms to the requirements prescribed therefor by this section. If such batch or any part thereof is to be packaged with a solvent, such request shall also be accompanied by a statement that such solvent conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; potency, sterility, moisture, and pH of the solution prepared as directed in its labeling.

(ii) The bacitracin used in making the batch; potency, toxicity, moisture, pH, and ash content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request in the quantities hereinafter indicated accurately representative samples of the following:

(i) The batch:

(*a*) For all tests except sterility; one immediate container for each 5,000 immediate containers in the batch, but in no case less than 5 immediate containers.

(*b*) For sterility testing; 10 immediate containers.

Such samples shall be collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The bacitracin used in making the batch; 6 packages, each containing approximately equal portions of not less than 500 milligrams packaged in accordance with the requirements of § 146e.401 (b).

(iii) In case of an initial request for certification, each other ingredient used in making the batch; one package of each, containing approximately 5.0 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container or package in the samples submitted in accordance with paragraph (d) (3) (i) (*a*), (ii), and (iii) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (i) (*b*) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 146e.409 Bacitracin-polymyxin ointment; zinc bacitracin-polymyxin ointment.

(a) Bacitracin - polymyxin ointment and zinc bacitracin-polymyxin ointment conform to all requirements and are subject to all procedures prescribed by § 146e.402 for bacitracin ointment and zinc bacitracin ointment, except paragraph (f) of that section, and except that:

(1) Its content of bacitracin or zinc bacitracin is not less than 200 units per gram.

(2) It contains not less than 4,000 units of polymyxin B per gram. The polymyxin B used conforms to the requirements prescribed for polymyxin B by § 146b.107 (a) of this chapter, except the standard for toxicity.

(3) Its moisture content is not more than 0.5 percent.

(4) If it is in liquid form, it shall be packaged in immediate containers of transparent glass which meet the test for tight containers as defined by the U. S. P.

(5) Its expiration date shall be the date that is 12 months after the month during which the batch was certified, except that if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for 18 months, 24 months, or 36 months at room temperature such drug as prepared by him complies with the standards of identity, strength, quality, and purity prescribed for the drug, the expiration date blank shall be filled in with the date that is 18 months, 24 months, or 36 months after the month during which the batch was certified.

(6) In addition to complying with the requirements of § 146e.402 (c), if it is in liquid form, each package shall bear on the outside wrapper or container and the immediate container, the statements "Shake well" and "Not for injection."

(7) In addition to complying with the requirements of § 146e.402 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and date of the latest tests and assays of the polymyxin used in making the batch for potency. He shall also submit in connection with his request a sample consisting of not less than 6 packages of ointment and (unless it was previously submitted) a sample consisting of 5 packages containing equal portions of not less than 0.5 gram each of the polymyxin used in making the batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (7) of this section shall be:

(1) $5.00 for each tube of ointment.

(2) $4.00 for each immediate container of the polymyxin used in making the batch.

§ 146e.410 Bacitracin-neomycin tablets; zinc bacitracin-neomycin tablets; bacitracin methylene disalicylate-neomycin tablets.

(a) Bacitracin-neomycin tablets, zinc bacitracin-neomycin tablets, and bacitracin methylene disalicylate-neomycin tablets conform to all requirements and are subject to all procedures prescribed for bacitracin tablets, zinc bacitracin tablets, and bacitracin methylene disalicylate tablets, except that:

(1) Each tablet contains not less than 2,500 units of bacitracin, zinc bacitracin, or bacitracin methylene disalicylate.

(2) Each tablet contains not less than 25 milligrams of neomycin. The neomycin used is produced by the growth of Streptomyces fradiae, has a potency of not less than 330 micrograms (one Waksman unit is equivalent to 3.3 micrograms of the base) per milligram, is nontoxic, has a moisture content of not more than 8 percent, and its pH in an aqueous solution 33 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(3) [Reserved.]

(4) In addition to complying with the requirements of § 146e.403 (d), a person who requests certification of a batch shall submit with his request a statement showing the number of units of bacitracin, zinc bacitracin, or bacitracin methylene disalicylate and the number of milligrams of neomycin in each tablet of the batch, the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, toxicity, moisture, and pH. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making such batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of this section shall be:

(1) $1.00 for each tablet.

(2) $4.00 for each immediate container in the sample of neomycin submitted.

§ 146e.411 Bacitracin-neomycin ointment; zinc bacitracin-neomycin ointment.

(a) Bacitracin-neomycin ointment and zinc bacitracin-neomycin ointment conform to all requirements and are subject to all procedures prescribed by § 146e.402 for bacitracin ointment and zinc bacitracin ointment, except paragraph (f) of that section, and except that:

(1) It contains not less than 3.50 milligrams of neomycin per gram. The neomycin used conforms to the requirements prescribed for neomycin by § 146e.410(a)(2), except the standard for toxicity.

(2) Its expiration date shall be the date that is 12 months after the month during which the batch was certified, except that if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for 18 months, 24 months, or 36 months at room temperature such drug as prepared by him complies with the standards of identity, strength, quality, and purity prescribed for the drug, the expiration date blank shall be filled in with the date that is 18 months, 24 months, or 36 months after the month during which the batch was certified.

(3) In addition to complying with the requirements of § 146e.402 (d), a person requesting certification of a batch shall submit with his request a statement showing the number of units of bacitracin or zinc bacitracin and the number of milligrams of neomycin in each gram of ointment, the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, moisture, and pH. He shall also submit in connection with his request a sample consisting of not less than 6 packages of the ointment and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making such batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (a) (3) of this section shall be:

(1) $5.00 for each immediate container of ointment.

(2) $4.00 for each immediate container of neomycin.

§ 146e.412 Bacitracin-polymyxin tablets.

(a) Bacitracin-polymyxin tablets conform to all requirements prescribed by § 146e.403 for bacitracin tablets, and are subject to all procedures prescribed by § 146e.403 for bacitracin tablets except that:

(1) Each tablet contains not less than 400 units of bacitracin.

(2) Each tablet contains not less than 8,000 units of polymyxin B sulfate. The polymyxin B used conforms to the requirements prescribed for polymyxin by § 146b.107 (a) of this chapter.

(3) [Reserved.]

(4) In addition to complying with the requirements of § 146e.403 (d) a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the polymyxin B used in making the batch for potency and toxicity. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages, each containing approximately equal portions of not less than 0.5 gram of the polymyxin B used in making the batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (4) of this section shall be:

(1) $1.00 for each tablet.

(2) $4.00 for each immediate container of polymyxin.

§ 146e.413 Bacitracin-neomycin troches; zinc bacitracin-neomycin troches.

Bacitracin-neomycin troches and zinc bacitracin-neomycin troches conform to all requirements and are subject to all procedures prescribed by § 146e.410 for bacitracin-neomycin tablets, except that:

(a) Each troche contains not less than 200 units of bacitracin or zinc bacitracin. The zinc bacitracin used conforms to the requirements prescribed by § 146e.418 (a).

(b) Each troche contains not less than 2.5 milligrams of neomycin.

(c) Each troche may be tableted with or without one or more suitable and harmless local anesthetics, preservatives, and chemical antimicrobial agents.

(d) In addition to the labeling prescribed for bacitracin-neomycin tablets, if it contains one or more of the ingredients specified in paragraph (c) of this section, each package shall bear on the outside wrapper or container and the immediate container the name and quantity of each such ingredient in each troche of the batch.

(e) If zinc bacitracin is used in the manufacture of the batch, the person who requests certification of a batch shall submit with his request results and the dates of the latest tests of the zinc bacitracin used in making the batch for potency, toxicity, moisture, pH, and zinc content. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 6 packages, each containing approximately 1.0 gram of the zinc bacitracin used in making the batch.

(f) The fee for the services rendered with respect to each package of the sample submitted in accordance with paragraph (e) of this section shall be $4.00.

§ 146e.414 Bacitracin-neomycin with vasoconstrictor; bacitracin-neomycin with _____ (the blank being filled in with the common or usual name of the vasoconstrictor).

(a) Bacitracin-neomycin with vasoconstrictor conforms to all requirements prescribed by § 146e.405 for bacitracin with vasoconstrictor and is subject to all procedures prescribed by § 146e.405 for bacitracin with vasoconstrictor, except that:

(1) When prepared as directed in its labeling it contains not less than 3.5 milligrams of neomycin per milliliter. The neomycin used conforms to the requirements prescribed for neomycin by § 146e.410 (a) (2).

(2) In lieu of the labeling prescribed by § 146e.405(c)(1)(i), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months or 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time. Furthermore, in lieu of the 1-week storage statement for the solution prescribed by § 146e.405(c)(1)(ii)(*b*), the labeling may bear a 3-week storage statement if the person who requests certification has submitted to the Commissioner results of tests and assays showing that solutions of the drug as prepared by him are stable for such period of time after storage at room temperature.

(3) In addition to complying with the requirements of § 146e.405 (d), a person who requests certification of a batch of bacitracin-neomycin with vasoconstrictor shall submit with his request a statement showing the number of units of bacitracin and the number of milligrams of neomycin in each immediate container, the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, toxicity, moisture, and pH. He shall also submit in connection with his request a sample consisting of not less than 6 packages of the bacitracin-neomycin with vasoconstrictor and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making such batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (3) of this section shall be:

(1) $5.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of the neomycin used in making the batch.

§ 146e.415 Bacitracin-polymyxin troches; zinc bacitracin-polymyxin troches.

Bacitracin-polymyxin troches and zinc bacitracin-polymyxin troches conform to all requirements and are subject to all procedures prescribed by § 146e.404 for bacitracin troches and zinc bacitracin troches, except that:

(a) Each troche contains not less than 50 units of bacitracin or zinc bacitracin.

(b) Each troche contains not less than 1,000 units of polymyxin B sulfate.

The polymyxin B used conforms to the requirements prescribed for polymyxin by § 146b.107 (a) of this chapter.

(c) Each troche may be tableted with or without one or more suitable and harmless local anesthetics.

(d) In addition to the labeling prescribed for bacitracin troches and zinc bacitracin troches, each package shall bear on its label or labeling the number of units of polymyxin B; and if it contains one or more local anesthetics, the name and quantity of each such ingredient in each troche of the batch.

(e) In addition to complying with the requirements of § 146e.404 (d), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the polymyxin B used in making the batch for potency and toxicity. He shall also submit in connection with his request (unless it was previously submitted) a sample consisting of 5 packages, each containing approximately equal portions of not less than 500 milligrams of the polymyxin used in making the batch.

(f) The fee for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (e) of this section are:

(1) $1.00 for each troche.

(2) $4.00 for each immediate container of the polymyxin used in making the batch.

§ 146e.416 Bacitracin methylene disalicylate.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin methylene disalicylate is the methylene disalicylate salt of a kind of bacitracin. It is so purified and dried that:

(1) Its potency is not less than 14 units per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 5 percent.

(4) Its pH in a saturated aqueous solution is not less than 3.5 and not more than 5.0.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. The composition of the immediate containers shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of bacitracin methylene disalicylate shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of units of bacitracin per gram, the number of grams of bacitracin activity per pound, and the weight of the drug in the immediate container.

(iii) The statement "Expiration date ----------," the blank being filled in with the date which is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date which is 36 months or 48 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time.

(iv) The statement "For veterinary use only."

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of units of bacitracin activity per gram, and the number of grams of bacitracin activity per pound. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, and pH.

(2) Such person shall submit with his request an accurately representative sample of the batch, consisting of 5 packages each containing approximately 5 grams taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigation.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.417 Powder bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.

(a) *Standards of identity, strength, quality, and purity.* Powder bacitracin methylene disalicylate and streptomycin sulfate oral veterinary is a mixture of bacitracin methylene disalicylate and streptomycin sulfate oral veterinary, with or without one or more suitable and harmless adsorbent ingredients, diluents, colorings, and flavorings. Each gram contains not less than 200 units of bacitracin activity and not less than 20 milligrams of streptomycin activity. Its moisture content is not more than 7.5 percent. The bacitracin methylene disalicylate used conforms to the requirements prescribed by § 146e.416(a). The streptomycin sulfate oral veterinary used conforms to the standards prescribed by § 146b.114(a) of this chapter. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. and shall be of such composition that they will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of units of bacitracin activity and the number of milligrams of streptomycin activity per gram and the total number of grams in the immediate container.

(iii) The statement "Expiration date ---------," the blank being filled in with the date which is 24 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(iv) The statement "For oral veterinary use only."

(v) If it contains adsorbent ingredients, the name of each.

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity. Such circular or other labeling may also bear a statement that a brochure or other printed matter containing information for other veterinary uses of such drug by a veterinarian licensed by law to administer it will be sent to such veterinarian on request.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch marks and (unless they were previously submitted) the dates on which the latest assays of the bacitracin methylene disalicylate and streptomycin sulfate oral veterinary used in making such batch were completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each other ingredient used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; units of bacitracin activity per gram, milligram of streptomycin activity per gram, and moisture.

(ii) The bacitracin methylene disalicylate and the streptomycin sulfate oral veterinary used in making the batch; potency, toxicity, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 6 immediate containers, unless each such container is packaged to contain more than 30 grams, in which case the sample shall consist of 30 grams for each 5,000 immediate containers in the batch, but in no case less than six 30-gram portions. Such samples shall be collected by taking single immediate containers or 30-gram portions at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The bacitracin methylene disalicylate used in making the batch; 5 packages containing approximately equal portions of not less than 5 grams each, packaged in accordance with the requirements of § 146e.416 (b).

(iii) The streptomycin sulfate oral veterinary used in making the batch; 5 packages containing approximately equal portions of not less than 1.0 gram each, packaged in accordance with the requirements of § 146b.114 (b) of this chapter.

(iv) In case of an initial request for certification, the other ingredients used in making the batch; 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) and (iii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section; $5.00 for each immediate container submitted in accordance with paragraph (d) (3) (i) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with the requirements of § 146.8 (d) of this chapter.

§ 146e.418 Zinc bacitracin (bacitracin zinc salt).

(a) *Standards of identity, strength, quality, and purity.* Zinc bacitracin is the zinc salt of a kind of bacitracin or a mixture of two or more such salts. It is so purified and dried that:

(1) Its potency is not less than 40 units per milligram.

(2) It is nontoxic.

(3) Its moisture content is not more than 5 percent.

(4) Its pH is not less than 6.0 and not more than 7.5.

(5) Its zinc content is not more than 10 percent by weight on a moisture-free basis.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. The composition of the immediate containers shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package of zinc bacitracin shall bear on its outside wrapper or container and the immediate container:

(1) The batch mark.

(2) The number of units of bacitracin activity per milligram of zinc bacitracin and the number of grams of the drug in the immediate container.

(3) The statement "Expiration date ------," the blank being filled in with the date which is 24 months after the month during which the batch was certified.

(4) The statement "For use only in the manufacture of nonparenteral drugs."

(5) The statement "Caution: Federal law prohibits dispensing without prescription."

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in the batch, the number of units of bacitracin activity per milligram of zinc bacitracin, the zinc content, and the total number of grams of zinc bacitracin in each package. Such request shall be accompanied or followed by the results of tests and assays made by him on the batch for potency, toxicity, moisture, pH, and zinc content.

(2) Such person shall also submit with his request an accurately representative sample of the batch, consisting of 5 packages each containing approximately 1.0 gram taken from a different part of such batch, and each shall be packaged in accordance with the requirements of paragraph (b) of this section.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (2) of this section.

(2) If the Commissioner considers that investigations other than the examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.419 Bacitracin-neomycin-polymyxin troches; zinc bacitracin-neomycin-polymyxin troches.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin-neomycin-polymyxin troches and zinc bacitracin-neomycin-polymyxin troches are troches composed of bacitracin or zinc bacitracin, neomycin, and polymyxin B with one or more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. The potency of each troche is not less than 200 units of bacitracin or zinc bacitracin, 5.0 milligrams of neomycin, and 2,000 units of polymyxin B. Its moisture content is not more than 5 percent. The bacitracin used conforms to the standards prescribed therefor by § 146e.401(a), except § 146e.401(a) (2), (4), and (8). The zinc bacitracin used conforms to the standards prescribed therefor by § 146e.418(a). The neomycin used conforms to the standards prescribed therefor by § 146e.410(a)(2). The polymyxin B used conforms to the standards prescribed therefor by § 146b.107(a) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(c) *Labeling.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the outside wrapper or container and the immediate container the statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, 36 months, 48 months, or 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed therefor by paragraph (a) of this section.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch

mark and (unless they were previously submitted) the dates on which the latest assays of the bacitracin or zinc bacitracin, neomycin, and polymyxin B used in making such batch were completed, the potency of each troche, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch; average potency of bacitracin or zinc bacitracin, neomycin, and polymyxin per troche, and average moisture.

(ii) The bacitracin used in making the batch; potency, toxicity, moisture, pH, and ash content.

(iii) The zinc bacitracin used in making the batch; potency, toxicity, moisture, pH, and zinc content.

(iv) The neomycin used in making the batch; potency, toxicity, moisture, and pH.

(v) The polymyxin used in making the batch; potency and toxicity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch; 1 troche for each 5,000 troches in the batch, but in no case less than 30 troches, collected by taking single troches at such intervals throughout the entire time of tableting that the quantities tableted during the intervals are approximately equal.

(ii) The bacitracin used in making the batch; 6 packages, each containing approximately equal portions of not less than 0.5 gram, packaged in accordance with the requirements of § 146e.401 (b).

(iii) The zinc bacitracin used in making the batch; 6 packages, each containing approximately equal portions of not less than 1.0 gram, packaged in accordance with the requirements of § 146e.418 (b).

(iv) The neomycin used in making the batch; 5 packages, each containing approximately equal portions of not less than 0.5 gram.

(v) The polymyxin used in making the batch; 5 packages, each containing approximately equal portions of not less than 0.5 gram.

(vi) In case of an initial request for certification, each other ingredient used in making the batch; 1 package of each, containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii), (iii), (iv), and (v) of this paragraph, and no samples referred to in subparagraph (3) (ii), (iii), (iv), and (v) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $1.00 for each troche in the sample submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), (iv), (v), and (vi) of this section.

(2) If the Commissioner considers that investigations, other than examination of such troches and packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.420 Bacitracin-tyrothricin-neomycin troches; bacitracin-gramicidin-neomycin troches; zinc bacitracin-tyrothricin-neomycin troches; zinc bacitracin - gramicidin - neomycin troches.

Bacitracin - tyrothricin - neomycin troches, bacitracin-gramicidin-neomycin troches, zinc bacitracin-tyrothricin-neomycin troches, and zinc bacitracin-gramicidin-neomycin troches conform to all requirements and are subject to all procedures prescribed by § 146e.413 for bacitracin-neomycin troches or zinc bacitracin-neomycin troches, except that:

(a) Each troche contains not less than 50 units of bacitracin or zinc bacitracin.

(b) Each troche contains not less than 1 milligram of tyrothricin or 0.2 milligram of gramicidin.

(c) They may contain cortisone or a suitable derivative of cortisone and one or more suitable antitussive drugs.

(d) In addition to the labeling prescribed for bacitracin-neomycin troches and zinc bacitracin-neomycin troches, each package shall bear on the outside wrapper or container and the immediate container the number of milligrams of tyrothricin or the number of milligrams of gramicidin in each troche of the batch; and if it contains cortisone or a derivative of cortisone or one or more antitussive drugs, the name and quantity of each such substance.

(e) If it does not contain cortisone or a suitable derivative of cortisone, or one or more antitussive drugs, in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for use of the drug by the laity.

§ 146e.421 Bacitracin-neomycin-polymyxin tablet.

(a) Bacitracin - neomycin - polymyxin tablets conform to all requirements and are subject to all procedures prescribed by § 146e.412 for bacitracin-polymyxin tablets, except that:

(1) Each tablet contains not less than 6 milligrams of neomycin. The neomycin used conforms to the requirements prescribed therefor by § 146e.410 (a) (2).

(2) [Reserved.]

(3) In addition to complying with the requirements of § 146e.412 (a) (4), a person who requests certification of a batch shall submit with his request a statement showing the batch mark and (unless it was previously submitted) the results and the date of the latest tests and assays of the neomycin used in making the batch for potency, toxicity, moisture, and pH. He shall also submit in connection with his request a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the neomycin used in making such batch.

(b) The fee for the services rendered with respect to each immediate container in the sample of neomycin submitted in accordance with the requirements prescribed therefor by this section shall be $4.00.

§ 146e.422 Bacitracin - polymyxin - neomycin ointment.

(a) Bacitracin - polymyxin - neomycin ointment conforms to all requirements prescribed by § 146e.409 for bacitracin-polymyxin ointment, and is subject to all procedures prescribed by § 146e.409 for bacitracin-polymyxin ointment, except that:

(1) Its content of neomycin is not less than 3.0 milligrams per gram. The neomycin used conforms to the standards prescribed by § 146e.410(a)(2), except the standard for toxicity.

(2) It may contain one or more suitable and harmless chemical antimicrobial agents.

(3) In addition to the labeling prescribed by § 146e.409 (a) (5), each package shall bear on the outside wrapper or container and the immediate container the number of milligrams of neomycin in each gram of the batch.

(4) In addition to complying with the requirements of § 146e.409 (a) (7), a person who requests certification of a batch of bacitracin-polymyxin-neomycin ointment shall submit with his request a statement showing the batch mark and (unless they were previously submitted) the results and date of the latest tests and assays of the neomycin used in making the batch for potency, moisture, and pH. He shall also submit in connection with his request a sample consisting of not less than 7 packages of bacitracin-polymyxin-neomycin ointment and (unless it was previously submitted) a sample consisting of 5 packages of the neomycin used in making the batch, each containing approximately 0.5 gram.

(b) The fee for the services rendered with respect to the samples submitted in accordance with the requirements of paragraph (a) (4) of this section shall be:

(1) $6.00 for each immediate container of ointment.

(2) $4.00 for each immediate container of the neomycin used in making the batch.

§ 146e.423 Soluble bacitracin methylene disalicylate.

(a) *Standards of identity, strength, quality, and purity.* Soluble bacitracin methylene disalicylate is a mixture of bacitracin methylene disalicylate, sodium carbonate, and sodium bicarbonate, with or without suitable and harmless diluents. It contains the equivalent of not less than 25 grams of the bacitracin master standard per pound. Its moisture content is not more than 8.5 percent. Its pH in an aqueous solution containing 200 units per milliliter is not less than 8.5 and not more than 9.5. The bacitracin methylene disalicylate used conforms to the requirements of § 146e.416(a). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees.* Soluble bacitracin methylene disalicylate conforms to all requirements and procedures prescribed for bacitracin methylene disalicylate by § 146e.416 (b), (c), (d), and (e), except that the person who requests certification of a batch shall submit with his request (unless previously submitted) a sample consisting of 5 immediate containers, each containing approximately 5 grams, of the bacitracin methylene disalicylate used in making the batch.

(c) *Exemption of soluble bacitracin methylene disalicylate from certification.* Soluble bacitracin methylene disalicylate that conforms to the requirements of paragraphs (a) (except that it may contain one or more essential vitamin and mineral substances for nutritive purposes) and (b) of this section shall be exempt from the requirements of sections 502 (l) and 507 of the act if it complies with all the following conditions:

(1) Its label bears an expiration date that is not more than 24 months after the month during which the batch was last assayed and released by the manufacturer.

(2) If it contains added vitamins or minerals, its label bears the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The label bears a statement that solutions prepared with the drug are stable for not more than 24 hours.

(4) The circular or other labeling within or attached to the package bears information that only the antibiotic is intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Chronic respiratory disease (airsac infection) in chickens.

(ii) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(iii) Infectious sinusitis in poultry.

(iv) Bacterial enteritis in swine.

§ 146e.424 Bacitracin-neomycin-polymyxin with vasoconstrictor; bacitracin-neomycin-polymyxin with _____ (the blank being filled in with the common or usual name of the vasoconstrictor).

(a) Bacitracin - neomycin - polymyxin with vasoconstrictor conforms to all requirements and is subject to all procedures prescribed by § 146e.414 for bacitracin-neomycin with vasoconstrictor, except that:

(1) When prepared as directed in its labeling, each milliliter shall contain not less than 50 units of bacitracin 3.5 milligrams of neomycin, and 1,000 units of polymyxin B. The polymyxin B used conforms to the requirements prescribed for polymyxin B by § 146b.107 (a) of this chapter.

(2) It may contain the enzyme hyaluronidase.

(3) It may be a packaged combination of one immediate container of dry components of the drug and one immediate container of a solution of components of the drug; but in no case shall bacitracin or hyaluronidase be a component of such solution of the packaged combination.

(4) The moisture content of the dry components of the drug is not more than 2.5 percent.

(5) [Reserved.]

(6) On the label or labeling, if it contains hyaluronidase, after the name "bacitracin - neomycin - polymyxin with vasoconstrictor," wherever it appears, the words "and hyaluronidase," shall appear in juxtaposition with such name.

(7) In addition to complying with the requirements of § 146e.414 (a) (3), a person who requests certification of a batch shall submit with his request a statement showing the number of units of polymyxin B in each immediate container, the batch mark, and (unless it was previously submitted) the results and the date of the latest tests and assays of the polymyxin used in making the batch for potency and toxicity. He shall also submit in connection with his request a sample consisting of not less than 7 packages of the bacitracin-neomycin-polymyxin with vasoconstrictor, and (unless it was previously submitted) a sample consisting of 5 packages containing approximately equal portions of not less than 0.5 gram each of the polymyxin used in making the batch.

(b) The fees for the services rendered with respect to the samples submitted in accordance with paragraph (a) (7) of this section shall be:

(1) $6.00 for each immediate container of the batch.

(2) $4.00 for each immediate container of the polymyxin used in making the batch.

§ 146e.425 Bacitracin powder.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin powder is bacitracin, with or without suitable and harmless buffer substances, preservatives, diluents, colorings, and flavorings. It contains the equivalent of not less than 10 grams of the bacitracin master standard per pound. Its moisture content is not more than 5 percent. The bacitracin used conforms to the standards prescribed therefor by § 146e.401(a), except § 146e.401(a) (2), (4), and (8). Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U. S. P. The composition of the immediate containers shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of units of bacitracin per gram, the number of grams of bacitracin activity per pound, and the weight of the drug in the immediate container.

(iii) The statement "Expiration date _____," the blank being filled in with the date that is 18 months after the month during which the batch was certified.

(iv) The statement "For oral veterinary use only."

(2) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless it was previously submitted) the date on which the latest assay of the bacitracin used in making such batch was completed, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each other ingredient used conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: Units of bacitracin per gram, and moisture.

(ii) The bacitracin used in making the batch: Potency, toxicity, moisture, pH, and ash content.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: 1 immediate container for each 5,000 immediate containers in the batch, but in no case less than 6 immediate containers, unless each such container is packaged to contain more than 30 grams, in which case the sample shall consist of 30 grams for each 5,000 immediate containers in the batch, but in no case less than six 30-gram portions or more than twelve 30-gram portions. Such samples shall be collected by taking single immediate containers or 30-gram portions at such intervals throughout the entire time of packaging

the batch that the quantities packaged during the intervals are approximately equal.

(ii) The bacitracin used in making the batch: 6 packages, each containing approximately equal portions of not less than 500 milligrams, packaged in accordance with the requirements of § 146e.401 (b).

(iii) In case of an initial request for certification, each other substance used in making the batch: 1 package of each containing approximately 5 grams.

(4) No result referred to in subparagraph (2) (ii) of this paragraph, and no sample referred to in subparagraph (3) (ii) of this paragraph, is required if such result or sample has been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $4.00 for each immediate container in the samples submitted in accordance with paragraph (d) (3) (i), (ii), and (iii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with the requirements of § 146.8 (d) of this chapter.

(f) *Exemption of bacitracin powder from certification.* Bacitracin powder that conforms to the requirements of paragraphs (a) (except that it may contain one or more essential vitamin and mineral substances for nutritive purposes), (b), and (c) of this section, except paragraph (c) (1) (iii), shall be exempt from the requirements of sections 502 (l) and 507 of the act if it complies with all the following conditions:

(1) Its label bears an expiration date that is not more than 18 months after the month during which the batch was last assayed and released by the manufacturer.

(2) If it contains added vitamins or minerals, its label bears the name and quantity of each such substance and a statement that such substances are present only for furnishing additional vitamins and minerals while animals are eating less feed.

(3) The label bears a statement that solutions prepared with the drug are stable for not more than 24 hours.

(4) The circular o. other labeling referred to in paragraph (c) (2) of this section bears information that only the antibiotic is intended for the prevention or treatment of the following conditions, and further, bears directions and warnings adequate for such use:

(i) Chronic respiratory disease (air-sac infection) in chickens.

(ii) Blue comb (mud fever, nonspecific infectious enteritis) in poultry.

(iii) Infectious sinusitis in poultry.

(iv) Bacterial enteritis in swine.

§ 146e.426 Tablets bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.

Tablets bacitracin methylene disalicylate and streptomycin sulfate oral veterinary are tablets that conform to all requirements and are subject to all procedures prescribed by § 146e.417 for powder bacitracin methylene disalicylate and streptomycin sulfate oral veterinary, except that:

(a) Each tablet shall contain not less than 150 units of bacitracin activity and not less than 15 milligrams of streptomycin activity. Tablets not exceeding 15 millimeters in diameter, or not intended only for preparing solutions, shall disintegrate within 1 hour.

(b) In lieu of the directions for labeling prescribed by § 146e.417 (c) (1) (ii), each package shall bear on the outside wrapper or container and the immediate container the quantity of each antibiotic in each tablet.

(c) In lieu of the directions for sampling the batch as prescribed in § 146e.417(d) (3) (i), the batch shall be sampled as follows:

(1) For potency and moisture: One tablet for each 5,000 tablets in the batch, but in no case less than 30 tablets, collected by taking single tablets throughout the entire time of tableting so that the quantities tableted during the intervals are approximately equal.

(2) For disintegration-time studies: 6 tablets.

(d) The fees for the services rendered with respect to the tablets submitted in accordance with the requirements prescribed therefor by paragraph (c) of this section shall be:

(1) $1.00 for each tablet submitted in accordance with paragraph (c) (1) of this section.

(2) $3.00 for all tablets submitted in accordance with paragraph (c) (2) of this section.

§ 146e.427 Feed grade bacitracin powder oral veterinary (crude bacitracin powder oral veterinary, unrefined bacitracin powder oral veterinary); feed grade zinc bacitracin powder oral veterinary (crude zinc bacitracin powder oral veterinary, unrefined zinc bacitracin powder oral veterinary).

(a) *Standards of identity, strength, quality, and purity.* Feed grade bacitracin powder oral veterinary is bacitracin with or without one or more essential vitamins and mineral substances for nutritive purposes and with or without one or more suitable and harmless diluents. Feed grade zinc bacitracin powder oral veterinary is a mixture of zinc bacitracin and zinc proteinates, with or without one or more essential vitamins and mineral substances for nutritive purposes and with or without one or more suitable and harmless diluents. They contain the equivalent of not less than 2.5 grams of the bacitracin master standard per pound, except that if it is zinc bacitracin powder it contains the equivalent of not less than 5 grams of the bacitracin master standard per pound. Their moisture content is not more than 5 percent. The bacitracin used in making the batch has a potency of not less than 5 units per milligram, and its moisture content is not more than 5 percent. The zinc bacitracin used in making the batch has a potency of not less than 2 units per milligram, not more than 2 grams of zinc for each gram of bacitracin, and its moisture content is not more than 6 percent. Each other substance used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees; exemption of feed grade bacitracin powder oral veterinary and feed grade zinc bacitracin powder oral veterinary from certification.* Feed grade bacitracin powder oral veterinary and feed grade zinc bacitracin powder oral veterinary conform to all requirements and procedures prescribed for bacitracin powder by § 146e.425 (b), (c), (d), (e), and (f), except that, if it is feed grade zinc bacitracin powder oral veterinary its expiration date is not more than 24 months after the month during which the batch was last assayed and released to the manufacturer.

§ 146e.428 Capsules bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.

Capsules bacitracin methylene disalicylate and streptomycin sulfate oral veterinary are capsules that conform to all requirements and are subject to all procedures prescribed by § 146e.426 for tablets bacitracin methylene disalicylate and streptomycin sulfate oral veterinary.

§ 146e.429 Bacitracin-neomycin in oil veterinary.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin-neomycin in oil veterinary is a suspension of bacitracin and neomycin in refined peanut oil or sesame oil, with or without one or more suitable and harmless chemical antimicrobial agents, anesthetics, and suspending agents. Each milliliter contains 200 units of bacitracin and 25 milligrams of neomycin, or each dose as recommended in its labeling shall contain 2,000 units of bacitracin and 250 milligrams of neomycin. Its moisture content is not more than 1.0 percent. The bacitracin used conforms to the requirements of § 146e.401 (a), except § 146e.401 (a) (2), (3), and (4). The neomycin used conforms to the requirements for potency, moisture, and pH prescribed for neomycin by § 146e.410 (a) (2). Each other ingredient used, if its name is recognized in the U. S. P. or N. F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* It shall be packaged in collapsible tubes that are well-closed containers as defined by the U.S.P. or in glass containers that are tight containers as defined by the U.S.P. The composition of the immediate container and closure shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unfavorable in good packag-

ing, storage, and distribution practice shall be disregarded.

(c) *Labeling.* Each package shall bear on its label or labeling as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The number of units of bacitracin and the number of milligrams of neomycin per milliliter or per immediate container.

(iii) If the batch contains, in addition to bacitracin and neomycin, one or more other active ingredients specified in paragraph (a) of this section, the name and quantity of each such other ingredient per milliliter or per immediate container.

(iv) The name of the oil and the suspending agent, if any, used in making the batch.

(v) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months or 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such period of time: *Provided however,* That such expiration date may be omitted from the immediate container if it contains a single dose and is packaged in an individual wrapper or container.

(vi) If it is packaged in a container of glass, the statements "For intramammary infusions of cattle only" and "Shake well."

(2) On the label and labeling, if it contains, in addition to bacitracin and neomycin, one or more other active ingredients specified in paragraph (a) of this section, after the name "bacitracin-neomycin in oil veterinary," wherever such name appears, the words "with ----------," in juxtaposition with such name, the blank being filled in with the common or usual name of each such other ingredient used.

(3) On the circular or other labeling within or attached to the package, adequate directions and warnings for the veterinary use of such drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch marks and (unless previously submitted) the dates on which the latest assays of the bacitracin and neomycin used in making such batch were completed, the number of units of bacitracin and the number of milligrams of neomycin in each milliliter, the quantity of each ingredient used in making the batch, the date on which the latest assay of the batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following, made by him on an accurately representative sample of:

(i) The batch: The number of units of bacitracin and the number of milligrams of neomycin per milliliter or per immediate container, and moisture.

(ii) The bacitracin used in making the batch: Potency, moisture, and pH.

(iii) The neomycin used in making the batch: Potency, moisture, and pH.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated, accurately representative samples of the following:

(i) The batch: One package for each 5,000 packages in the batch, but in no case less than six packages, collected by taking single packages at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) The bacitracin used in making the batch: Six packages, each containing approximately equal portions of not less than 500 milligrams, packaged in accordance with the requirements of § 146e.401 (b).

(iii) The neomycin used in making the batch: Five packages, each containing approximately equal portions of not less than 0.5 gram.

(iv) In case of an initial request for certification, each other ingredient used in making the batch: One package of each, containing approximately 200 grams.

(4) The results referred to in subparagraph (2) (ii) and (iii) of this paragraph and the samples referred to in subparagraph (3) (ii) and (iii) of this paragraph are not required if such results or samples have been previously submitted.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this chapter shall be:

(1) $5.00 for each package in the sample submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each package in the samples submitted in accordance with paragraph (d) (3) (ii), (iii), and (iv) of this section.

(2) If the Commissioner considers that investigations, other than examination of such packages, are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.430 Bacitracin-neomycin-polymyxin powder topical; zinc bacitracin-neomycin-polymyxin powder topical.

(a) *Standards of identity, strength, quality, and purity.* Bacitracin-neomycin-polymyxin powder topical and zinc bacitracin-neomycin-polymyxin powder topical are bacitracin or zinc bacitracin, neomycin, and polymyxin B, with or without suitable and harmless diluents, preservatives, and lubricants, and with or without hyaluronidase, chymotrypsin, and polyvinylpyrrolidone. Unless it is packaged with one or more suitable and harmless inert gases, each gram contains not less than 200 units of bacitracin or zinc bacitracin, not less than 1,600 units of polymyxin B, and not less than 3.5 milligrams of neomycin. It contains not more than an average of 10 microorganisms per gram. Its moisture content is not more than 7.0 percent, unless it is packaged with one or more suitable and harmless inert gases, in which case its moisture content is not more than 0.5 percent. The bacitracin used conforms to the standards prescribed therefor by § 146e.401(a), except § 146e.401(a) (2) and (4). The zinc bacitracin used conforms to the standards prescribed by § 146e.418(a). The neomycin used conforms to the standards prescribed therefor by § 146e.410(a)(2). The polymyxin B used conforms to the standards prescribed therefor by § 146b.-107(a) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U. S. P. The composition of the immediate container shall be such as will not cause any change in the strength, quality, or purity of the contents beyond any limits therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each such container may contain one or more suitable and harmless inert gases; in which case it shall contain not less than 8,000 units of zinc bacitracin, not less than 70 milligrams of neomycin, and not less than 100,000 units of polymyxin B.

(c) *Labeling*—(1) *It is packaged for dispensing and intended for use by man.* In addition to the labeling requirements prescribed by § 1.106(b) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container:

(*a*) The statement "Expiration date ----------," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, or 24 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section,

(*b*) The statement "Not sterile."

(ii) If it contains, in addition to the antibiotic drug, one or more other active

ingredients specified in paragraph (a) of this section, after the name "bacitracin-neomycin-polymyxin powder topical" or "zinc bacitracin-neomycin-polymyxin powder topical," wherever such name appears, the words "with _____," in juxtaposition with such name, the blank being filled in with the common or usual name of each such other ingredient.

(2) *It is packaged for dispensing and intended solely for veterinary use.* Its label and labeling shall comply with all the requirements prescribed by subparagraph (1) of this paragraph, except that in lieu of the statement "Caution: Federal law prohibits dispensing without prescription" each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark and (unless they were previously submitted) the dates on which the latest assays of the bacitracin or zinc bacitracin, neomycin, and polymyxin used in making such batch were completed, the number of units of bacitracin or zinc bacitracin and polymyxin B, and the number of milligrams of neomycin in each immediate container, the date on which the latest assays of the drugs comprising such batch were completed, the quantity of each ingredient used in making the batch, and a statement that each such ingredient conforms to the requirements prescribed therefor by this section.

(2) Except as otherwise provided in subparagraph (4) of this paragraph, such person shall submit in connection with his request results of the tests and assays listed after each of the following made by him on an accurately representative sample of:

(i) The batch: The number of units of bacitracin or zinc bacitracin, the number of units of polymyxin, and the number of milligrams of neomycin, a microorganism count, and moisture.

(ii) The bacitracin or zinc bacitracin used in making the batch: Potency, toxicity, moisture, pH, and zinc content if it is zinc bacitracin.

(iii) The neomycin used in making the batch: Potency, toxicity, moisture, and pH.

(iv) The polymyxin B used in making the batch: Potency and toxicity.

(3) Except as otherwise provided by subparagraph (4) of this paragraph, such person shall submit in connection with his request, in the quantities hereinafter indicated accurately representative samples of the following:

(i) The batch: For all tests except microorganism count, one immediate container for each 5,000 immediate containers in the batch, but in no case less than seven immediate containers, collected by taking single immediate containers at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) For microorganism testing: Five immediate containers.

(iii) The bacitracin or zinc bacitracin used in making the batch: Six packages, containing approximately equal portions of not less than 0.5 gram.

(iv) The neomycin used in making the batch: Five packages containing approximately equal portions of not less than 0.5 gram.

(v) The polymyxin B used in making the batch: Five packages containing approximately equal portions of not less than 0.5 gram.

(vi) In case of an initial request for certification, each other substance used in making the batch: One package of each containing approximately 5 grams.

(4) The results referred to in subparagraph (2) (ii), (iii), and (iv) of this paragraph and the samples referred to in subparagraph (3) (iii), (iv), (v), and (vi) of this paragraph are not required if such results or samples have been previously submitted.

(e) *Fees.* The fees for the services rendered with respect to each batch under the regulations in this part shall be:

(1) $6.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3) (i) of this section; $4.00 for each immediate container in the sample submitted in accordance with paragraph (d) (3), (iii), (iv), (v), and (vi) of this section; $10.00 for all containers submitted in accordance with paragraph (d) (3) (ii) of this section.

(2) If the Commissioner considers that investigations other than examination of such immediate containers are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8 (d) of this chapter.

§ 146e.431 Feed grade manganese bacitracin powder oral veterinary.

(a) *Standards of identity, strength, quality, and purity.* Feed grade manganese bacitracin powder oral veterinary is a mixture of the manganese salt of a kind of bacitracin or a mixture of two or more such salts, with or without one or more essential vitamins and mineral substances for nutritive purposes and with or without one or more suitable and harmless diluents. It contains the equivalent of not less than 5 grams of the bacitracin master standard per pound. Its moisture content is not more than 8.0 percent. The manganese bacitracin used in making the batch has a potency of not less than 2.0 units per milligram, it contains not more than 1.0 gram of manganese for each gram of bacitracin, and its moisture content is not more than 6.0 percent. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(b) *Packaging; labeling; request for certification, samples; fees; exemption of feed grade manganese bacitracin powder oral veterinary from certification.* Feed grade manganese bacitracin powder oral veterinary conforms to all requirements and procedures prescribed for feed grade zinc bacitracin powder oral veterinary by § 146e.427(b), except:

(1) Its expiration date shall be 12 months.

(2) Its labeling is such that when it is mixed with animal feed according to the directions contained therein such medicated feed complies with the requirements of § 146.13, for manganese bacitracin medicated feed.

PART 147—ANTIBIOTICS INTENDED FOR USE IN THE LABORATORY DIAGNOSIS OF DISEASE

Sec.

147.1 Antibiotic sensitivity discs; tests and methods of assay; potency.
147.2 Antibiotic sensitivity discs; certification procedure.
147.3 Antibiotic–dehydrated media–triphenyltetrazolium chloride sensitivity discs; tests and methods of assay.
147.4 Antibiotic–dehydrated media–triphenyltetrazolium chloride sensitivity discs; certification procedure.

AUTHORITY: §§ 147.1 to 147.4 issued under sec. 701, 52 Stat. 1055, as amended; 21 U.S.C. 371. Interpret or apply sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357.

§ 147.1 Antibiotic sensitivity discs; tests and methods of assay; potency.

(a) *Culture media.* Use ingredients that conform to the standards prescribed by the United States Pharmacopeia or The National Formulary. In lieu of preparing the media from the individual ingredients, they may be made from a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such media. Minor modification of the specified individual ingredients is permissible if the resulting media possess growth-promoting properties at least equal to the media described.

(1) *Medium A:*

Peptone	6.0 gm.
Pancreatic digest of casein	4.0 gm.
Yeast extract	3.0 gm.
Beef extract	1.5 gm.
Dextrose	1.0 gm.
Agar	15.0 gm.
Distilled water, q. s.	1,000.0 ml.

pH 6.5 to 6.6 after sterilization.

(2) *Medium B.* Same as medium A, except that it also contains 300 milligrams of hydrated manganese sulfate per liter.

(3) *Medium C.* Same as medium A, except that the final pH is adjusted from 7.9 to 8.1 after sterilization.

(4) *Medium D:*

Peptone	5.0 gm.
Yeast extract	1.5 gm.
Beef extract	1.5 gm.
Sodium chloride	3.5 gm.
Dextrose	1.0 gm.
Dipotassium phosphate	3.68 gm.
Potassium dihydrogen phosphate	1.32 gm.
Distilled water, q. s.	1,000.0 ml.

pH 7.0 after sterilization.

(5) *Medium E:*

Peptone	6.0 gm.
Yeast extract	3.0 gm.
Beef extract	1.5 gm.
Agar	15.0 gm.
Distilled water, q. s.	1,000.0 ml.

pH 6.5 to 6.6 after sterilization.

(6) *Medium F:*

Pancreatic digest of casein	17.0 gm.
Papaic digest of soybean	3.0 gm.
Sodium chloride	5.0 gm.
Dipotassium phosphate	2.5 gm.
Dextrose	2.5 gm.
Agar	20.0 gm.
Distilled water, q.s.	1,000.0 ml.

pH 7.3 after sterilization.

(7) *Medium G.* Same as medium F, except for the following:

Agar	12.0 gm.
Polysorbate 80 (sterile)	10.0 gm.

Add polysorbate 80 after boiling.

(8) *Medium H:*

Peptone	9.4 gm.
Yeast extract	4.7 gm.
Beef extract	2.4 gm.
Sodium chloride	10.0 gm.
Dextrose	10.0 gm.
Agar	23.5 gm.
Distilled water, q.s.	1,000.0 ml.

pH 6.0 to 6.2 after sterilization.

(b) *Preparation of test organism suspensions*—(1) *Suspension 1.* Staphylococcus aureus (ATCC 6538P) is maintained and grown on medium A. Wash the organisms from an agar slant, incubated for 24 hours at 32° C. to 35° C., with 3.0 milliliters of sterile sodium chloride solution onto the agar surface of a Roux bottle containing 300 milliliters of medium A. Spread the suspension of organisms over the entire agar surface with the aid of sterile glass beads. Incubate 24 hours at 32° C. to 35° C. Wash the resulting growth from the agar surface with about 50 milliliters of sterile sodium chloride solution. Standardize this stock suspension by determining the dilution that will permit 20 percent light transmission. Store the stock suspension in the refrigerator (1 week) and use the indicated dilution prepared daily.

(2) *Suspension 2.* Follow the procedure described for suspension 1, except standardize the bulk suspension so that a 1:10 dilution in saline solution gives 20 percent light transmission. In this case, the bulk suspension, and not the 1:10 dilution of it, is used for the inoculum.

(3) *Suspension 3.* The test organism is Staphylococcus aureus (ATCC 13150). Follow the procedure described for suspension 1, but determine how much the bulk suspension should be diluted to obtain a suspension permitting 80 percent light transmission. Use the indicated dilution prepared daily for the inoculum for the plates.

(4) *Suspension 4.* Sarcina lutea (ATCC 9341) is maintained on agar slants of medium A and transferred to fresh slants approximately every 2 weeks. This culture is incubated overnight at 26° C., and then stored in the refrigerator. Prepare an inoculum for the plates as follows: Streak an agar slant heavily with the test organism and incubate for 24 hours at 26° C. Wash the growth from the slant with 3 milliliters to 4 milliliters of medium D, and transfer to the surface of a Roux bottle containing 300 milliliters of medium A. Spread the suspension evenly over the entire surface with the aid of sterile glass beads. Incubate for 24 hours at 26° C. Wash the growth from the agar surface with 15 milliliters of medium D. If an aliquot of this bulk suspension when diluted 1:10 with medium D gives 10 percent light transmission, the bulk suspension is satisfactory for use. It may be necessary to adjust the bulk suspension by dilution so that an aliquot of the adjusted suspension when diluted 1:10 will give the desired 10 percent light transmission. The adjusted bulk suspension only, and not the 1:10 dilution of it, is used in preparing the inoculum. Store the stock suspension in the refrigerator and use for 2 weeks.

(5) *Suspension 5.* Bacillus subtilis (ATCC 6633) is maintained on agar medium A and transferred to a fresh slant every month. To prepare the spore suspension, inoculate a fresh slant of agar medium A with the test organism and incubate at 37° C. for 16 hours to 24 hours. Wash the culture from the slant with 3 milliliters of sterile sodium chloride solution onto the surface of a Roux bottle containing 300 milliliters of agar medium B. Incubate for 5 days at 37° C. Suspend the growth in 50 milliliters of sterile saline solution, centrifuge, and decant the supernatant liquid. Reconstitute the sediment and heat-shock the suspension by heating for 30 minutes at 70° C. Store the spore suspension in the refrigerator. It may be kept several months. Light transmission is not used for standardization.

(6) *Suspension 6.* Staphylococcus epidermidis (ATCC 12228) is maintained on medium A and transferred to a fresh slant once a week. Inoculate a fresh slant of medium A with the test organism and incubate at 32° C. to 35° C. for 24 hours. Wash the culture from the slant with 3 milliliters of sterile sodium chloride solution onto the surface of a Roux bottle containing 300 milliliters of medium A. Incubate at 32° C. to 35° C. for 24 hours. Wash the resulting growth from the agar surface with about 50 milliliters of sterile sodium chloride solution. Standardize this stock suspension by determining the dilution that will give 80 percent light transmission. Store the stock suspension in the refrigerator (1 week) and use the indicated dilution prepared daily for the inoculum for the plates.

(7) *Suspension 7.* Bordetella bronchiseptica (ATCC 4617) is maintained on medium F and transferred to a fresh slant every 2 weeks. To prepare a stock suspension inoculate a fresh slant of medium F and incubate at 37° C. for 16 hours to 24 hours. Wash the culture from this slant with 3 milliliters of sterile distilled water onto the surface of a Roux bottle containing 300 milliliters of medium F, and incubate 24 hours at 37° C. Wash off the growth with 50 milliliters of sterile distilled water and standardize the resulting stock suspension by determining the dilution that will give 50 percent light transmission. Store the stock suspension in the refrigerator (2 weeks), and use the indicated dilution prepared daily for the inoculum for the plates.

(8) *Suspension 8.* Saccharomyces cerevisiae (ATCC 9763) is maintained on slants of medium H and transferred once a week. After transfer, the culture is incubated at 37° C. for 24 hours and then kept refrigerated. Wash the organism from a freshly incubated agar slant with 3 milliliters of sterile saline solution onto the agar surface in a Roux bottle containing 300 milliliters of medium H. Spread the suspension of organisms over the entire agar surface with the aid of sterile glass beads. Incubate for 24 hours at 37° C. and then wash the resulting growth from the agar surface with about 25 milliliters of sterile saline solution. Store the suspension in the refrigerator and use for 1 month.

(9) *Suspension 9.* Follow the procedure described for suspension 1, except determine how much the bulk suspension should be diluted to obtain a suspension permitting 80 percent light transmission. Use the indicated dilution, prepared daily, for the inoculum for the plates.

The light transmission values referred to in this paragraph were determined with a Lumetron Model 400–A photoelectric colorimeter at a wavelength of 650 millimicrons. If other instruments are used, different light transmission readings will probably be obtained. The values given are to be used as guides in this paragraph.

(c) *Preparation of plates*—(1) *Base layer.* Depending on the particular antibiotic in the discs to be tested, add 42 milliliters of the appropriate medium prescribed in subparagraph (3) of this paragraph to each Petri dish (20 millimeters x 150 millimeters) and allow to harden on a flat, level surface and dry slightly by raising the tops on one side.

(2) *Seed layer.* Add the appropriate amount of inoculum, as prescribed by subpargaraph (3) of this paragraph, to the seed agar which has been melted and cooled to 48° C. Swirl the flasks to obtain a homogeneous suspension. Add 8 milliliters of the appropriate seed agar, as specified in subparagraph (3) of this paragraph, to each plate, spread evenly over the hardened base layer, and allow to harden and dry on a flat level surface. For accurate results, it is necessary to obtain uniform distribution of the agar over the surface of the plates.

(3) *Inoculum and media to be used.* Depending on the particular antibiotic in the disc to be tested, select from the following table the inoculum and media to be used:

Antibiotic	Volume of suspension added to each 100 ml. of seed agar used for test	Suspension number	Medium	
			Base layer	Seed layer
	Ml.			
Bacitracin	1.0	3	E	A
Carbomycin (hydrochloride)	1.5	2	E	A
Chloramphenicol	4.0	4	E	A
Chlortetracycline (hydrochloride)	1.5	4	E	A
Colistin (sulfate)	1.0	7	F	G
Demethylchlortetracycline (hydrochloride)	1.5	4	E	A
Dihydrostreptomycin (sulfate)	1.0	1	O	O
Methicillin	1.0	3	E	A
Erythromycin	2.0	2	O	O
Kanamycin (sulfate)	1.0	9	E	A
Neomycin B (sulfate)	2.0	6	E	A
Novobiocin (sodium)	4.0	5	E	A
Nystatin	0.1	8	H	H
Oleandomycin (phosphate)	2.0	2	E	A
Oxytetracycline (hydrochloride)	1.5	4	E	A
Penicillin G	1.0	3	E	A
Phenethicillin potassium	1.0	3	E	A
Polymyxin B (sulfate)	1.0	7	F	G
Ristocetin	0.5	4	A	A
Sodium oxacillin	1.0	3	E	A
Streptomycin (sulfate)	3.0	1	O	O
Tetracycline (hydrochloride)	1.5	4	E	A
Vancomycin	1.0	6	C	O
Viomycin (sulfate)	1.0	5	C	O

(d) *Preparation of control discs.* Use round, blank discs having a diameter of ¼-inch made of clear-white paper weighing 30 milligrams ±4 milligrams per square centimeter, and which will absorb 2.5 to 3.0 times its own weight of distilled water. The paper shall contain no material that either enhances or inhibits the activity of any antibacterial agent impregnated thereon. In addition, the paper shall contain no materials which will affect the pH of any solvent placed on it or buffer any solution placed on it. The following methods shall be used to determine the suitability in this regard of any paper proposed for this use: Weigh 2 grams of paper or paper discs into a clean, glass-stoppered, 250-milliliter flask. Add 30 milliliters of freshly boiled and cooled distilled water (the pH of which has been determined). Stopper and shake vigorously for 1 hour on a shaking machine. Filter through a medium-porosity sintered glass filter. Determine the pH of the filtrate. Take the two 10-milliliter aliquots. To one add 0.05 milliliter of 0.01 *N* HCl. To the second aliquot add 0.05 milliliter of 0.01 *N* NaOH. Determine the pH of each solution. The paper shall be satisfactory for use, if (1) the pH of the paper filtrate was not more than ±0.3 pH units different from the pH of the distilled water used; (2) the pH of the acidified aliquot was lowered by at least 1.0 pH units; (3) the pH of the alkalinized aliquot was raised by at least 1.5 pH units. Place blank discs on aluminum or stainless steel wire mesh which is supported in a manner to allow circulation of air above and below the discs. Prepare the desired number of discs for each point on the standard curve by accurately adding 0.02-milliliter-increments of the appropriate standard stock solution to each disc, using a suitable pipette. Dry discs in circulating air or under vacuum. Discs may be stored for 2 weeks in a desiccator under refrigeration. Depending on the antibiotic contained in the sample to be tested, prepare the stock solutions for the standard discs by dissolving an accurately weighed quantity of the working standard in the solvent indicated to obtain stock solutions that will contain the following concentrations required for the standard discs:

Antibiotic	Solvent	Standard curve (antibiotic concentration per disc)
Bacitracin	Water	1.3, 2.4, 4.4, 8.1, 15.0 units.
Carbomycin (hydrochloride)	Methyl alcohol	1.3, 2.7, 5.4, 11.0, 22.5μg.
Chloramphenicol	50 percent methyl alcohol	3.3, 6.3, 12.2, 23.4, 45.0μg.
Chlortetracycline (hydrochloride)	Methyl alcohol	3.3, 6.3, 12.2, 23.4, 45.0μg.
Colistin (sulfate)	Water	1.3, 2.4, 4.4, 8.1, 15.0μg.
Demethylchlortetracycline (hydrochloride)	Methyl alcohol	3.3, 6.3, 12.2, 23.4, 45.0μg.
Dihydrostreptomycin	Water	1.3, 2.4, 4.4, 8.1, 15.0μg.
Methicillin	do	1.3, 2.4, 4.4, 8.1, 15.0μg.
Erythromycin	Methyl alcohol	1.3, 2.7, 5.4, 11.0, 22.5μg.
Kanamycin (sulfate)	Water	3.3, 6.3, 12.2, 23.4, 45.0μg.
Neomycin B (sulfate)	do	3.3, 6.3, 12.2, 23.4, 45.0μg.
Novobiocin (sodium)	do	3.3, 6.3, 12.2, 23.4, 45.0μg.
Nystatin	Dimethylformamide pH 6.5±0.5	64, 80, 100, 125, 156 units.
Oleandomycin (phosphate)	Water	1.3, 2.7, 5.4, 11.0, 22.5μg.
Oxytetracycline (hydrochloride)	Methyl alcohol	3.3, 6.3, 12.2, 23.4, 45.0μg.
Penicillin G	Water	1.3, 2.4, 4.4, 8.1, 15.0 units.
Phenethicillin potassium	do	1.3, 2.4, 4.4, 8.1, 15.0 units.
Polymyxin B (sulfate)	do	33, 63, 122, 234, 450 units.
Ristocetin	do	3.3, 6.3, 12.2, 23.4, 45.0μg.
Sodium oxacillin	do	0.67, 0.82, 1.00, 1.22, 1.5μg.
Streptomycin (sulfate)	do	1.3, 2.4, 4.4, 8.1, 15.0μg.
Tetracycline (hydrochloride)	Methyl alcohol	3.3, 6.3, 12.2, 23.4, 45.0μg.
Vancomycin (hydrochloride)	Water	3.3, 6.3, 12.2, 23.4, 45.0μg.
Viomycin (sulfate)	do	1.3, 2.4, 4.4, 8.1, 15.0μg.

(e) *Assay*—(1) *Individual discs one-fourth inch in diameter.* On each of three plates prepared as directed in paragraph (c) of this section, place the five control discs for the standard curve and two discs from each batch to be tested. The control discs for the standard curve and the sample discs are placed on the plates in a random arrangement, with no discs being closer than 24 millimeters (on centers) to any other disc. Discs are placed on the plates with the aid of forceps within as short a period of time as possible (not to exceed 3 minutes per plate) and tapped gently to ensure an even seal. Incubate the plates overnight at 32° C–35° C., except if it is polymyxin, novobiocin, nystatin, viomycin, or colistin, the incubation temperature is 37° C. After incubation, measure the diameter of each circle of inhibition, using calipers or a measuring device of comparable accuracy. Average the three zone sizes for each of the five standard-curve concentrations and plot the mean sizes on the arithmetic scale of semilogarithmic graph paper with the antibiotic concentrations on the logarithmic scale. Use the following equation to calculate the best straight line.

$$L=\frac{3a+2b+c-e}{5},$$

$$H=\frac{3e+2d+c-a}{5},$$

where

L=the calculated zone size of the low concentration;

H=the calculated zone size of the high concentration;

a, b, c, d, e=the observed average zone sizes for each respective concentration, a being that for the lowest concentration.

Plot the values obtained for L and H and connect these two points with a straight line. Average the six sample zone sizes and read the corresponding antibiotic concentration of this mean from the standard curve. This is the average potency of the sample disc.

(2) *Discs one-fourth inch in diameter attached to rings, spokes, or other devices.* Remove or cut the disc from the device, including a small portion of the device to which it is attached, before testing, and proceed as directed in subparagraph (1) of this paragraph.

(3) *Individual discs with diameters larger than one-fourth inch but no larger than three-eighths inch.* Proceed as directed in subparagraph (1) of this paragraph, except instead of measuring the diameters of the zones of inhibition, measure the widths of the zones from any edge of the sample discs and the standard discs. The results obtained are multiplied by the factor 2 for determining whether the discs meet the requirements for uniformity prescribed by paragraph (f) of this section.

(4) *Discs having diameters larger than one-fourth inch but no greater than three-eighths inch attached to rings, spokes, or other devices.* Remove or cut the disc from the device, including a small portion of the device to which it

is attached, before testing, and proceed as directed in subparagraph (3) of this paragraph, except measure the width of the zone of inhibition from the rounded tip of the disc.

(f) The potency is satisfactory if the result obtained is not less than 67 percent and not more than 150 percent of that represented. The batch has a uniform potency if on the first or second test of six discs each, the diameter of the largest zone of inhibition is not more than 2.5 millimeters larger than the smallest zone, or if the number of zones that fall outside this range in three or more consecutive tests is not more than 10 percent of the total number of discs tested.

§ 147.2 Antibiotic sensitivity discs; certification procedure.

(a) *Standards of identity, strength, quality, and purity.* Antibiotic sensitivity discs are paper or plastic discs or compressed tablets containing penicillin G, methicillin, oxacillin, phenethicillin, streptomycin, dihydrostreptomycin, chlortetracycline, demethylchlortetracycline, tetracycline, chloramphenicol, or bacitracin. If they are tablets they may contain suitable lubricants, binders, and diluents, none of which shall affect the antibacterial spectrums of the antibiotics. Each disc shall have a uniform potency that is equivalent to that contained in a standard disc prepared with one of the following quantities of antibiotic compounds:

(1) Bacitracin: Not less than two units or not more than 10 units.

(2) Chloramphenicol: Not less than 5 μg or not more than 30 μg.

(3) Chlortetracycline: Not less than 5 μg or not more than 30 μg.

(4) Dihydrostreptomycin: Not less than 2 μg or not more than 10 μg.

(5) Penicillin G: Not less than two units or not more than 10 units.

(6) Streptomycin: Not less than 2 μg or not more than 10 μg.

(7) Tetracycline: Not less than 5 μg or not more than 30 μg.

(8) Demethylchlortetracycline: Not less than 5 μg or not more than 30 μg.

(9) Methicillin: 5 μg.

(10) Oxacillin: 1 μg.

(11) Phenethicillin potassium: 3 units.

The standard discs used to determine the potency shall be made of paper as described in § 147.1(d). Each antibiotic compound used to impregnate such standard discs shall be equilibrated in terms of the working standard designated by the Commissioner for use in determining the potency or purity of such antibiotic.

(b) *Packaging.* The immediate container shall be a tight container as defined by the U.S.P., and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. Each immediate container may contain a desiccant, and each may be packaged in combination with containers of suitable discs of drugs other than those described in paragraph (a) of this section. Such other discs shall be suitable only if the manufacturer and packer have submitted to the Commissioner information of the kind described in § 146.7 of this chapter and such information has been accepted by the Commissioner. If a packaged combination contains discs of more than one potency of any one of the antibiotics included in paragraph (a) of this section, the potencies shall be only the lowest and highest concentrations prescribed for that antibiotic by that paragraph.

(c) *Labeling.* Each package of discs shall bear on its label or labeling, as hereinafter indicated, the following:

(1) On the outside wrapper or container and the immediate container:

(i) The batch mark.

(ii) The potency of each disc in the batch.

(iii) The statement "Expiration date _____," the blank being filled in with one of the following appropriate dates after the month during which the batch was certified:

(*a*) For penicillin G, methicillin, oxacillin, and phenethicillin potassium: 6 months, except 12 months may be used if the person who requests certification has submitted to the Commissioner results of tests and assays showing that such drug as prepared by him is stable for such time.

(*b*) For bacitracin: 12 months.

(*c*) For streptomycin, dihydrostreptomycin, chlortetracycline, demethylchlortetracycline, tetracycline, and chloramphenicol: 24 months.

If it is a packaged combination of discs of two or more drugs, its outside wrapper shall bear only one expiration date, and that date shall be the date that is required for the shortest dated discs contained in the package.

(iv) The statement "For use in laboratory diagnosis only."

(2) On the circular or other labeling within or attached to the package, adequate directions for the use of such discs.

(d) *Request for certification; samples.* (1) In addition to complying with the requirements of § 146.2 of this chapter, a person who requests certification of a batch of antibiotic sensitivity discs shall submit with his request a statement showing the batch mark, the number of packages of each size in such batch, the batch mark, and, unless it was previously submitted, the date on which the latest assay of the antibiotic used in making such batch was completed, the potency of each disc, the quantity of each ingredient used in making the batch, the date on which the latest assay of the drug comprising such batch was completed, and a statement that each ingredient used in making the batch conforms to the requirements prescribed therefor by this section.

(2) Such person shall submit in connection with his request results of the tests and assays made by him on an accurately representative sample of the batch for potency.

(3) Such person shall submit in connection with his request an accurately representative sample of the batch consisting of one disc for each 5,000 discs in the batch, but in no case less than 36 discs collected by taking single discs at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(e) *Fees.* The fee for the services rendered with respect to each batch under the regulations in this section shall be:

(1) $0.30 for each disc in the sample submitted in accordance with paragraph (d)(3) of this section.

(2) If the Commissioner considers that investigations other than the examination of such discs and packages are necessary to determine whether or not such batch complies with the requirements of § 146.3 of this chapter for the issuance of a certificate, the cost of such investigations.

The fee prescribed by subparagraph (1) of this paragraph shall accompany the request for certification unless such fee is covered by an advance deposit maintained in accordance with § 146.8(d) of this chapter.

§ 147.3 Antibiotic-dehydrated media-triphenyltetrazolium chloride sensitivity discs; tests and methods of assay.

(a) *Potency.* Proceed as directed in § 147.1, except paragraph (f) of that section and except that:

(1) In the assay of kanamycin, neomycin, and oleandomycin, use the following inoculum and media:

Antibiotic	Suspension added to each 100 ml. of seed agar used for test	Suspension number	Medium	
			Base layer	Seed layer
	Milliters			
Kanamycin	1.0	9	C	C
Neomycin	1.0	9	C	C
Oleandomycin	2.0	3	C	C

(2) Each disc used for the standard curve shall have a diameter of one-half inch.

(3) Prepare an aqueous stock solution as follows, and sterilize by filtration:

Dehydrated brain-heart infusion	6.105 gm.
Dibasic sodium phosphate	1.410 gm.
Yeast extract	3.300 gm.
Dextrose	1.645 gm.
Sodium lactate (about 60 percent) syrup	2.750 ml.
Triphenyltetrazolium chloride	1.2375 gm.
Polysorbate 80	0.75 ml.
Distilled water, q.s.	1,000.0 ml.

pH 7.35 ±0.05 after sterilization.

(4) Use the solution described in subparagraph (3) of this paragraph to prepare the antibiotic stock solution, which shall contain per 0.06 milliliter the appropriate concentrations for the standard curve. In the case of chloramphenicol and erythromycin, the antibiotics shall be first dissolved in methyl alcohol to a concentration of an estimated 10,000 μg. per milliliter.

(5) Add 0.06 milliliter increments of the appropriate stock solution to the discs used for the standard curve.

(6) In addition to the five antibiotic control discs for the standard curve, place on the agar surface one of the antibiotic-free discs used in making the batch. If any zone of inhibition is produced by the antibiotic-free disc, it must be smaller than that produced by the disc containing the lowest concentration of antibiotic, and it shall not be used in the equation for calculating the best straight line.

(7) If the sample discs are curled, press them flat prior to placement on agar. When placing them on agar, tap lightly to insure that they lie evenly on the surface.

(8) Its potency is satisfactory if the disc contains not less than 67 percent and not more than 150 percent of that represented and if any zone of inhibition that may be produced by the antibiotic-free disc of the batch is smaller than that produced by each of the antibiotic-dehydrated media-triphenyltetrazolium chloride discs.

(b) *Performance*—(1) *Culture medium.* Prepare the following medium: (In lieu of the individual ingredients, it may be made from a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such medium.)

Calf brains, infusion from	200 gm.
Beef heart, infusion from	250 gm.
Proteose peptone	10 gm.
Dextrose	2 gm.
Salt	5 gm.
Sodium phosphate monobasic (Na_2HPO_4)	2.5 gm.
Distilled water, q.s.	1,000.0 ml.

pH 7.4 after sterilization.

(2) *Preparation of test organism suspensions.* Maintain the following test organisms on slants of Medium E as described in § 147.1(a)(5), and transfer to fresh agar slants once weekly:

Organisms	*A.T.C.C. No.*
Pseudomonas aeruginosa	14504
Streptococcus faecalis	14508
Proteus rettgeri	14505
Streptococcus faecalis	14506
Streptococcus faecalis	14507
Staphylococcus aureus	6538P
Staphylococcus epidermidis	12228

From fresh agar slants, inoculate separate portions of the medium described in subparagraph (1) of this paragraph and incubate 16 hours to 24 hours at 37° C. Prepare a 1–10 dilution of each of these fresh broth cultures, using the medium described in subparagraph (1) of this paragraph as the diluent.

(3) *Susceptible organisms.* Use the organism indicated for the following antibiotics:

Antibiotic	*Organism*
Penicillin G	Streptococcus faecalis, A.T.C.C. 14506.
Streptomycin	Pseudomonas aeruginosa, A.T.C.C. 14504.
Tetracycline	Streptococcus faecalis, A.T.C.C. 14506.
Chloramphenicol	Pseudomonas aeruginosa, A.T.C.C. 14504.
Bacitracin	Streptococcus faecalis, A.T.C.C. 14507.
Erythromycin	Streptococcus faecalis, A.T.C.C. 14506.
Kanamycin	Proteus rettgeri, A.T.C.C. 14505.
Neomycin	Staphylococcus epidermidis, A.T.C.C. 12228.
Novobiocin	Streptococcus faecalis, A.T.C.C. 14506.
Oleandomycin	Streptococcus faecalis, A.T.C.C. 14506.
Polymyxin B	Pseudomonas aeruginosa, A.T.C.C. 14504.
Ristocetin	Streptococcus faecalis, A.T.C.C. 14506.

(4) *Resistant organisms.* Use the organism indicated for the following antibiotics:

Antibiotic	*Organism*
Penicillin G	Pseudomonas aeruginosa, A.T.C.C. 14504.
Streptomycin	Proteus rettgeri, A.T.C.C. 14505.
Tetracycline	Streptococcus faecalis, A.T.C.C. 14508.
Chloramphenicol	Proteus rettgeri, A.T.C.C. 14505.
Bacitracin	Proteus rettgeri, A.T.C.C. 14505.
Erythromycin	Streptococcus faecalis, A.T.C.C. 14508.
Kanamycin	Streptococcus faecalis, A.T.C.C. 14507.
Neomycin	Streptococcus faecalis, A.T.C.C. 14506.
Novobiocin	Proteus rettgeri, A.T.C.C. 14505.
Oleandomycin	Proteus rettgeri, A.T.C.C. 14505.
Polymyxin B	Proteus rettgeri, A.T.C.C. 14505.
Ristocetin	Pseudomonas aeruginosa, A.T.C.C. 14504.

(5) *Procedure for the tests.* To three replicate discs, aseptically add 0.15 milliliter of the sensitive organism suspension described in subparagraph (3) of this paragraph. To three additional discs, aseptically add 0.15 milliliter of the resistant organism suspension described in subparagraph (4) of this paragraph. In the same manner, add the sensitive organism suspension to three antibiotic-free discs used in making the batch, and add the resistant organism suspension to three additional such discs. If the batch is packaged in multiple-disc containers, use sterile, clear glass or plastic culture dishes for the tests. If the batch is packaged in containers that are intended for use in the clinical performance of the test, such containers shall be used for these tests. Immediately place in incubator at 37° C. and incubate for 6 hours. (During this period, do not expose the discs to light.) After incubation, observe the discs. The sample is satisfactory if the control discs and the three discs inoculated with the resistant organism suspension have changed to a definite shade of red or purple; and if the three discs inoculated with the sensitive organism suspension have undergone no change, or appreciably less change, in comparison to the change in color in the antibacterial-free control disc inoculated with the same organism suspension.

(c) *Sterility.* To each of six discs, aseptically add 0.15 milliliter of the medium described in paragraph (b)(1) of this section. If the batch is packaged in multiple-disc containers, use sterile, clear glass or plastic culture dishes for this test. If it is packaged in containers that are intended for use in the clinical performance of the test, use such containers for this test. Immediately place in incubator and incubate overnight at 37° C. (During this period do not expose the discs to light.) The sample is satisfactory if no discs have changed color.

§ 147.4 Antibiotic-dehydrated media-triphenyltetrazolium chloride sensitivity discs; certification procedure.

Antibiotic-dehydrated media-triphenyltetrazolium chloride sensitivity discs are discs that conform to all requirements and to all procedures prescribed by § 147.2 for antibiotic sensitivity discs, except the requirement for uniformity, and except that:

(a)(1) Each disc shall contain penicillin G, streptomycin, tetracycline, chloramphenicol, or bacitracin. If it is tetracycline, it shall contain 5 micrograms.

(2) Each disc shall be impregnated with the microbial growth-supporting solution described in § 147.3(a)(3).

(3) Under the conditions of use, no (or appreciably less) change in comparison to the change in color in the control disc shall occur when the disc is tested against a sensitive organism, but its color shall change to definite shades of red or purple when tested against a resistant organism.

(4) The disc shall be sterile.

(5) Each disc shall have a diameter of one-half inch.

(b) In all cases, the immediate container shall be sterile at the time of filling and closing. If it is a packaged combination, such package shall contain only those discs described in paragraph (a) of this section, with or without discs, of one or more of the following antibiotics: Erythromycin, kanamycin, neomycin, novobiocin, oleandomycin, polymyxin B, and ristocetin. Such other discs shall conform to the standards prescribed by paragraph (a) of this section, except subparagraph (1).

(c) In addition to complying with the requirements of § 147.2(c), the label and labeling shall also bear:

(1) Information that the discs contain a dehydrated microbial growth-supporting medium and triphenyltetrazolium chloride.

(2) The statement "Keep under refrigeration."

(3) The statement "Expiration date ----------," the blank being filled in with the date that is 6 months after the month during which the batch was certified.

(d) In lieu of the requirements prescribed by § 147.2(d) (2) and (3), the person who requests certification of a batch shall submit in connection with his request:

(1) Results of the tests and assays made by him on an accurately representative sample of the batch for potency, performance, and sterility, and of

the medium and the triphenyltetrazolium chloride used in making the batch; and

(2) An accurately representative sample of the batch consisting of one disc for each 5,000 discs in the batch, but in no case less than 48 discs. Such discs shall be collected as follows:

(i) For potency testing: 24 discs collected by taking single discs at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal.

(ii) For performance testing: 12 discs collected as described in subdivision (i) of this subparagraph, except that if the immediate container is intended for use in the clinical performance of the test, such sample shall consist of 12 discs packed in their final immediate containers.

(iii) For sterility testing: Five immediate containers, except if the immediate container is intended for use in the clincial performance of the test, such sample shall consist of 12 discs packed in their final immediate containers.

(3) In addition to the samples required by subparagraph (2) of this paragraph, such person shall submit 36 discs that contain the solution described in § 147.3(a)(3) used in making the batch, but which do not contain the antibiotic.

(e) In lieu of the fee prescribed by § 147.2(e)(1), the fee shall be $0.35 for each disc of the samples submitted in accordance with paragraph (d)(2) (i) and (ii) of this section; $7.50 for all discs submitted in accordance with paragraph (d) (2)(iii) and (3) of this section.

Dated: December 18, 1962.

GEO. P. LARRICK,
Commissioner of Food and Drugs.

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